SECTION 1

GENERAL

1 Clinical pharmacy process

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Key points

- Clinical pharmacy comprises a set of functions that promote the safe, effective and economic use of medicines for individual patients.
- The emergence of clinical pharmacy has allowed pharmacists to shift from a product-oriented role towards direct engagement with patients and the problems they encounter with medicines.
- The practice of clinical pharmacy is generally an essential component of pharmaceutical care.
- Pharmaceutical care is a co-operative, patient-centred system for achieving specific and positive patient outcomes from the responsible provision of medicines.
- The three key elements of the care process are patient assessment, determining the care plan and evaluating the outcome.
- The ability to consult with patients is a key process in the delivery of pharmaceutical care and requires regular review and development regardless of experience.
- The clinical pharmacy process has been incorporated into a professional development framework that can be used to enhance skills and knowledge.

Clinical pharmacy, unlike the discipline of pharmacy, is a comparatively recent and variably implemented form of practice. It encourages pharmacists and support staff to shift their focus from a solely product-oriented role towards more direct engagement with patients and the problems they encounter with medicines. Over the past 20 years there has been an emerging consensus that the practice of clinical pharmacy itself should grow from a collection of patient-related functions to a process in which all actions are undertaken with the intention of achieving explicit outcomes for the patient. In doing so, clinical pharmacy moves to embrace the philosophy of pharmaceutical care (Hepler and Strand, 1990).

This chapter provides a practical framework within which a knowledge and understanding of therapeutics and practice can be best utilised. It describes a pragmatic approach to applying both the principles of pharmaceutical care and the specific skills of clinical pharmacy in a manner that does not depend on the setting of the practitioner or patient.

Development of clinical practice in pharmacy

The emergence of clinical pharmacy as a form of practice has been attributed to the poor medicines control systems that existed in hospitals during the early 1960s (Cousins and Luscombe, 1995). Although provoked by similar hospital-centred problems, the nature of the professional response differed between the USA and the UK.

In the USA, the approach was to adopt unit dose dispensing and pursue decentralisation of pharmacy services. In the UK, the unification of the prescription and the administration record meant this document needed to remain on the hospital ward and required the pharmacist to visit the ward to order medicines. Clinical pharmacy thereby emerged from the presence of pharmacists in these patient areas and their interest in promoting safer medicines use. This was initially termed 'ward pharmacy' but participation in medical ward rounds in the late 1970s signalled the transition to clinical pharmacy.

Medication safety may have been the spur but clinical pharmacy in the 1980s grew because of its ability to promote cost-effective medicines used in hospitals. This role was recognised by the UK government, which, in 1988, endorsed the implementation of clinical pharmacy services to secure value for money from medicines. Awareness that support depended, to an extent, on the quantification of actions and cost savings led several groups to develop ways of measuring pharmacists' clinical interventions. Coding systems were necessary to aggregate large amounts of data in a reliable manner and many of these drew upon the eight steps (Table 1.1) of the drug use process (DUP) indicators (Hutchinson et al., 1986).

The data collected from these early studies revealed that interventions had very high physician acceptance rates, were made most commonly at the 'select regimen' and 'need for drug' stages of the DUP, and were influenced by hospital ward type (intensive care and paediatrics having the highest rates), pharmacist grade (rates increasing with grade) and time spent on wards (Barber et al., 1997).

Despite the level of activity that intervention monitoring revealed, together with evidence of cost containment and a broadly supportive health care system, frustrations began to appear. These, in part, stemmed from a lack of certainty about the fundamental purpose of clinical pharmacy and

Table 1.1 Drug use process (DUP) indicators

DUP stage	Action
Need for a drug	Ensure there is an appropriate indication for each drug and that all medical problems are addressed therapeutically
Select drug	Select and recommend the most appropriate drug based upon the ability to reach therapeutic goals, with consideration of patient variables, formulary status and cost of therapy
Select regimen	Select the most appropriate drug regimen for accomplishing the desired therapeutic goals at the least cost without diminishing effectiveness or causing toxicity
Provide drug	Facilitate the dispensing and supply process so that drugs are accurately prepared, dispensed in ready-to-administer form and delivered to the patient on a timely basis
Drug administration	Ensure that appropriate devices and techniques are used for drug administration
Monitor drug therapy	Monitor drug therapy for effectiveness or adverse effects in order to determine whether to maintain, modify or discontinue
Counsel patient	Counsel and educate the patient or caregiver about the patient's therapy to ensure proper use of medicines
Evaluate effectiveness	Evaluate the effectiveness of the patient's drug therapy by reviewing all the previous steps of the drug use process and taking appropriate steps to ensure that the therapeutic goals are achieved

from tensions between the drive towards specialisation in clinical pharmacy and the need to improve services of a more general level in hospitals and other care settings.

Pharmaceutical care

The need to focus on outcomes of medicines use rather than dwelling only on the functions of clinical pharmacy became apparent (Hepler and Strand, 1990). The launch of pharmaceutical care as the 'responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life' was a landmark in the topography of pharmacy practice. In reality, this was an incremental step forward, rather than a revolutionary leap, since the foundations of pharmaceutical care as 'the determination of drug needs for a given individual and the provision not only of the drug required but also the necessary services to assure optimally safe and effective therapy' had been established previously (Brodie et al., 1980).

Table 1.2 Definitions of clinical pharmacy, pharmaceutical care and medicines management

Term	Definition
Clinical pharmacy	Clinical pharmacy comprises a set of functions that promote the safe, effective and economic use of medicines for individual patients. Clinical pharmacy process requires the application of specific knowledge of pharmacology, pharmacokinetics, pharmaceutics and therapeutics to patient care
Pharmaceutical care	Pharmaceutical care is a co-operative, patient-centred system for achieving specific and positive patient outcomes from the responsible provision of medicines. The practice of clinical pharmacy is an essential component in the delivery of pharmaceutical care
Medicines management	Medicines management encompasses the way in which medicines are selected, procured, delivered, prescribed, administered and reviewed to optimise the contribution that medicines make to producing informed and desired outcomes of patient care

The delivery of pharmaceutical care is dependent on the practice of clinical pharmacy but the key feature of care is that the practitioner takes responsibility for a patient's drug-related needs and is held accountable for that commitment. None of the definitions of pharmaceutical care is limited by reference to a specific professional group. Although pharmacists and pharmacy support staff would expect to, and clearly can, play a central role in pharmaceutical care, it is essentially a co-operative system that embraces the contribution of other professionals and patients (Table 1.2). The avoidance of factionalism has enabled pharmaceutical care to permeate community pharmacy, particularly in Europe, in a way that clinical pharmacy and its bedside connotations did not. It also anticipated health care policy in which certain functions, such as the prescribing of medicines, have been extended beyond their traditional professional origins to be undertaken by those trained and identified to be competent to do so.

Medication-related problems

When the outcome of medicines use is not optimal, a classification (Box 1.1) for identifying the underlying medication-related problem (MRP) has been proposed (Hepler and

Box 1.1 Categories of medication-related problems

Untreated indication
Treatment without indication
Improper drug selection
Too little drug
Too much drug
Non-compliance
Adverse drug reaction
Drug interaction

Strand, 1990). Some MRPs are associated with significant morbidity and mortality. Preventable medication-related hospital admissions in the USA have a prevalence of 4.3%, indicating that gains in public health from improved medicines management would be sizeable (Winterstein et al., 2002). In the UK too, preventable medication-related morbidity has been associated with 4.3% of admissions to a medical unit. In nearly all cases, the underlying MRP was linked to prescribing, monitoring or adherence (Howard et al., 2003).

In prospective studies, up to 28% of accident and emergency department visits have been identified as medication related, of which 70% are deemed preventable (Zed, 2005). Again, the most frequently cited causes were non-adherence and inappropriate prescribing and monitoring. The cost of drug-related morbidity and mortality in the US ambulatory care (outpatient) population was estimated in 2000 to be $177 billion. Hospital admission accounted for 70% of total costs (Ernst and Grizzle, 2001). In England, adverse drug reactions (ADRs) have been identified as the cause of 6.5% of hospital admissions for patients over 16 years of age. The median bed stay with patients admitted with an ADR was 8 days representing 4% of bed capacity. The projected annual cost to the NHS was £466 million, the equivalent of seven 800-bed hospitals occupied by patients admitted with an ADR (Pirmohamed et al., 2004).

The rate for adverse drug events among hospital inpatients in the USA has been quantified as 6.5 per 100 admissions. Overall, 28% of events were judged preventable, rising to 42% of those classified as life-threatening or serious (Bates et al., 1995). The direct cost of medication errors, defined as preventable events that may cause or lead to inappropriate medicines use or harm, in NHS hospitals has been estimated to lie between £200 and £400 million per year. To this should be added the costs arising from litigation (DH, 2004).

The scale of the misadventure that these findings reveal, coupled with increasing concerns about the costs of drug therapy, creates an opportunity for a renaissance in clinical pharmacy practice, providing that it realigns strongly with patient safety, cost-effectiveness and prevention of ill health. In practice, community pharmacists may be uniquely placed to help reduce the level of medication-related morbidity in primary care by virtue of their accessibility and existing relationships.

Benefits of pharmaceutical care

The ability to demonstrate that clinical pharmacy practice improves patient outcomes is of great importance to the pharmaceutical care model. In the USA, for example, pharmacists' participation in physician ward rounds has been shown to reduce adverse drug events by 78% and 66% in general medical (Kucukarslan et al., 2003) and intensive care settings (Leape et al., 1999), respectively. A study covering 1029 US hospitals was the first to indicate that both centrally based and patient-specific clinical pharmacy services are associated with reduced mortality rates (Bond et al., 1999). The services involved were medicines information, clinical research performed by pharmacists, active pharmacist participation in resuscitation teams and pharmacists undertaking admission medication histories.

In the UK, the focus has been also on prevention and management of medicine-related problems. Recognition that many patients either fail to benefit or experience unwanted effects from their medicines has elicited two types of response from the pharmacy profession. The first response has been to put in place, and make use of, a range of postgraduate initiatives and programmes to meet the developmental needs of pharmacists working in clinical settings. The second has been the re-engineering of pharmaceutical services to introduce schemes for medicines management at an organisational level. These have ranged from specific initiatives to target identified areas of medication risk, such as pharmacist involvement in anticoagulation services, to more general approaches where the intention is to ensure consistency of medicines use, particularly across care interfaces. Medicines reconciliation on hospital admission ensures that medicines prescribed to in-patients correspond to those that the patient was taking prior to admission. Guidance in the UK recommends that medicines reconciliation should be part of standard care and that pharmacists should be involved as soon as possible after the patient has been admitted (NICE and NPSA, 2007). Medicines reconciliation has been defined as:

- Collecting information on medication history using the most recent and accurate sources of information to create a full, and current, list of medicines;
- Verifying this list against the hospital drug chart and ensuring that any discrepancies are identified and acted upon;
- Documenting and communicating any changes, omissions or discrepancies.

This process requires the name of medicines, dosage, frequency and route of administration to be established for all medicines taken prior to admission. The information collected as part of medicines reconciliation is a pre-requisite for medication review, which is a process which considers the appropriateness of treatment and the patient's medication-taking behaviour.

Pharmaceutical consultation

Structured postgraduate education has served to improve the knowledge of clinical pharmacists but fully achieving the goals of pharmaceutical care has proved more challenging. Part of the difficulty has been the requirement to place the patient at the heart of the system, rather than being a relatively passive recipient of drug therapy and associated

information. To deliver pharmaceutical care requires more than scientific expertise. It mandates a system that describes the role and responsibilities of the pharmacist and provides the necessary infrastructure to support them in this role and, secondly, a clear process by which the pharmacist can deliver their contribution to patient care.

Pharmaceutical care is predicated on a patient-centred approach to identifying, preventing or resolving medicine-related problems. Central to this aim is the need to establish a therapeutic relationship. This relationship must be a partnership in which the pharmacist works with the patient to resolve medication-related issues in line with the patient's wishes, expectations and priorities. Table 1.3 summarises the three key elements of the care process (Cipolle et al., 1998). Research in chronic diseases has shown that self-management is promoted when patients more fully participate in the goal-setting and planning aspects of their care (Sevick et al., 2007). These are important aspects to consider when pharmacists consult with patients. In community pharmacy, one approach to help patients used their medicines more effectively is medicines use review (MUR). This uses the skills of pharmacists to help patients understand how their medicines should be used, why they take them and to identify any problems patients have in relation to their medicines, providing feedback to the prescriber if necessary. Two goals of MUR are to improve the adherence of patients to prescribed medicines and to reduce medicines wastage.

Clinical guidance on medicines adherence emphasises the importance of patient involvement in decisions about medicines (NICE, 2009).

Recommendations include that health care professionals should:

- adapt their consultation style to the needs of individual patients
- consider any factors which may affect patients' involvement in the consultation
- establish the most effective way of communicating with each patient
- encourage patients to ask about their condition and treatment
- be aware that consultation skills can be improved to enhance patient involvement.

Table 1.3 Key elements of the care process

Element	Purpose
Assessment	The main goal is to establish a full medication history and highlight actual and potential drug-related problems
Care plan	This should clearly state the goals to optimise care and the responsibilities of both the pharmacist and the patient in attaining the stated goals
Evaluation	This reviews progress against the stated patient outcomes

Medicines-taking behaviour

The need for a care process which ensures that the patient is involved at all stages has become clearer as the extent of non-adherence has been revealed. Significant proportions (between 30% and 50%) of patients with chronic conditions do not take their prescribed medicines as directed. Many factors are thought to influence a patient's decision to adhere to a prescribed regimen. These include the characteristics of the disease and the treatment used to manage it, the patient's beliefs about their illness and their medicines, as well as the quality of the interaction between the patient and health care practitioner. Non-adherence can be categorised broadly into two types: intentional and unintentional. Unintentional non-adherence may be associated with physical or sensory barriers to taking medicines, for example, not being able to swallow or unable to read the labels, forgetfulness or poor comprehension. Traditionally, pharmacists have played a key role in helping patients overcome these types of problems, but have been less active in identifying and resolving intentional non-adherence.

Intentional (or deliberate) non-adherence may be due to a number of factors. Recent work in health psychology has shaped our understanding of how patients perceive health and illness and why they often decide not to take their medicines. When people receive information about illness and its treatment, it is processed in accordance with their own belief systems. Often patients' perceptions are not in tune with the medical reality and when this occurs, taking medicines may not make sense to the individual. For example, a patient diagnosed with hypertension may view the condition as one that is caused by stress and, during periods of lower stress, may not take their prescribed medicines (Baumann and Leventhal, 1985). Consequently, a patient holding this view of hypertension may be at increased risk of experiencing an adverse outcome such as a stroke.

More recent research has shown that patient beliefs about the necessity of the prescribed medication and concerns about the potential long-term effects have a strong influence on medicines-taking behaviour (Horne, 2001). However, a patient's beliefs about the benefits and risks of medicines are rarely explored during consultation, despite evidence of an association between non-adherence and the patient's satisfaction with the consultation process adopted by practitioners (Ley, 1988).

Consultation process

There are several comprehensive accounts of the functions required to satisfy each stage of the DUP, but few go on to explore how the pharmacist might create a therapeutic relationship with their patient. The ability of a pharmacist to consult effectively is fundamental to pharmaceutical care and this includes establishing a platform for achieving adherence/concordance. Nurturing a relationship with the patient is essential to understanding their medication-related needs.

Descriptions of pharmaceutical consultation have been confined largely to the use of mnemonics such as WWHAM, AS METTHOD and ENCORE (Box 1.2). These approaches

provide the pharmacist with a rigid structure to use when questioning patients about their symptoms but, although useful, serve to make the symptom or disease the focus of the consultation rather than the patient. A common misconception is that health care professionals who possess good communication skills are also able to consult effectively with patients; this relationship will not hold if there is a failure to grasp the essential components of consultation technique. Research into patients' perceptions of their illness and treatment has demonstrated that they are more likely to adhere to their medication regimen, and be more satisfied with the consultation, if their views about illness and treatment have been taken into account and the risks and benefits of treatment discussed. The mnemonic approach to consultation does not address adequately the complex interaction that may take place between a patient and a health care practitioner.

Undertaking a pharmaceutical consultation can be considered as a series of four interlinked phases, each with a goal and set of competencies (Table 1.4). These phases follow a problem-solving pattern, embrace relevant aspects of adherence research and attempt to involve the patient at each stage in the process. For effective consultation, the practitioner also needs to draw upon a range of communication behaviours (Box 1.3). This approach serves to integrate the agendas of both patient and pharmacist. It provides the vehicle for agreeing on the issues to be addressed and the responsibilities accepted by each party in achieving the desired outcomes.

The ability to consult with patients is a key process in the delivery of pharmaceutical care and consequently requires regular review and development, regardless of experience. To ensure these core skills are developed, individuals should use trigger questions to prompt reflection on their approach to consulting (Box 1.4).

Box 1.2 Mnemonics used in the pharmacy consultation process

WWHAM
Who is it for?
What are the symptoms?
How long has it been going on?
Action taken?
Medicines taken?

AS METTHOD
Age of the patient?
Self or for someone else?
Medicines being taken?
Exactly what do you mean (by the symptom)?
Time and duration of the symptom
Taken any action (medicine or seen the doctor)?
History of any disease?
Other symptoms?
Doing anything to alleviate or worsen the symptom?

ENCORE
Evaluate the symptom, its onset, recurrence and duration.
No medication is always an option.
Care when dealing with specific patient groups, notably the elderly, the young, nursing mothers, pregnant women, those receiving specific medication such as methotrexate and anticoagulants, and those with particular disease, for example, renal impairment.
Observe the patient for signs of systemic disturbance and ask about presence of fever, loss of weight and any accompanying physiological disturbance.
Refer when in doubt.
Explain any course of action recommended.

Box 1.3 Consultation behaviours

Active listening
Appropriate use of open and closed questions
Respect patient
Avoid jargon
Demonstrate empathy
Deal sensitively with potentially embarrassing or sensitive issues

Table 1.4 Pharmaceutical consultation process

Element	Goal	Examples of associated competencies
Introduction	Building a therapeutic relationship	Invites patient to discuss medication or health-related issue Discusses structure and purpose of consultation Negotiates shared agenda
Data collection and problem identification	Identifying the patient's medication-related needs	Takes a full medication history Establishes patient's understanding of their illness Establishes patient's understanding of the prescribed treatment Identifies and prioritises patient's pharmaceutical problems
Actions and solutions	Establishing an acceptable management plan with the patient	Involves patient in designing management plan Tailors information to address patient's perception of illness and treatment Checks patient's understanding Refers appropriately
Closure	Negotiating safety netting strategies with the patient	Provides information to guide action when patient experiences problems with management plan Provides further appointment or contact point

Box 1.4 Key postconsultation questions

Do I know more now about the patient?
Was I curious?
Did I really listen?
Did I find out what really mattered to them?
Did I explore their beliefs and expectations?
Did I identify the patient's main medication-related problems?
Did I use their thoughts when I started explaining?
Did I share the treatment options with them?
Did I help my patient to reach a decision?
Did I check that they understood what I said?
Did we agree?
Was I friendly?

Clinical pharmacy functions and knowledge

The following practical steps in the delivery of pharmaceutical care are based largely on the DUP. The 'select regimen' and 'drug administration' indicators have been amalgamated at step 3.

Step 1. Establishing the need for drug therapy

For independent prescribers this step includes establishing a diagnosis and then balancing the risks and benefits of treatment against the risks posed by the disease. Current practice for most pharmacists means that another professional, most frequently a doctor, will have diagnosed the patient's presenting condition and any co-existing disease. The pharmacist's role, therefore, is often one of providing information to the independent prescriber on the expected benefits and risks of drug therapy by evaluating both the evidence base and individual patient factors. Pharmacists also draw on these concepts as they become more involved in prescribing and adjusting therapy for patients under their care.

The evidence for one specific mode of therapy may not be conclusive. In this circumstance, the pharmacist will need to call on their understanding of the principles of pharmaceutical science and on clinical experience to provide the best advice possible.

Step 1.1. Relevant patient details

Without background information on the patient's health and social circumstances (Table 1.5) it is difficult to establish the existence of, or potential for, MRPs. When this information is

Table 1.5 Relevant patient details

Factor	Implications
Age	The very young and the very old are most at risk of medication-related problems. A patient's age may indicate their likely ability to metabolise and excrete medicines and have implications for step 2 of the drug use process
Gender	This may alter the choice of the therapy for certain indications. It may also prompt consideration of the potential for pregnancy or breast feeding
Ethnic or religious background	Racially determined predispositions to intolerance or ineffectiveness should be considered with certain classes of medicines, for example, ACE inhibitors in Afro-Caribbean people. Formulations may be problematic for other groups, for example, those based on blood products for Jehovah's Witnesses or porcine-derived products for Jewish patients
Social history	This may impact on ability to manage medicines and influence pharmaceutical care needs, for example, living alone or in a care home or availability of nursing, social or informal carers
Presenting complaint	Symptoms the patient describes and the signs identified by the doctor on examination. Pharmacists should consider whether these might be attributable to the adverse effects of prescribed or purchased medicines
Working diagnosis	This should enable the pharmacist to identify the classes of medicines that would be anticipated on the prescription based on current evidence
Previous medical history	Understanding the patient's other medical conditions and their history helps ensure that management of the current problem does not compromise a prior condition and guides the selection of appropriate therapy by identifying potential contraindications
Laboratory or physical findings	The focus should be on findings that may affect therapy, such as • renal function • liver function • full blood count • blood pressure • cardiac rhythm Results may convey a need for dosage adjustment or presence of an adverse reaction

lacking a review solely of prescribed medicines will probably be of limited value and risks making a flawed judgement on the appropriateness of therapy for that individual.

Current and co-existing conditions with which the patient presents can be established from various sources. In medical notes, the current diagnosis (Δ) or differential diagnoses (ΔΔ) will be documented, as well as any previous medical history (PMH). Other opportunities to gather information come from discussion with the patient and participation in medical rounds. In primary care, general medical practitioners' computer systems carry information on the patient's diagnosis.

Once the diagnosis and PMH are established it is then possible to identify the medicines that would be expected to be prescribed for each indication, based on contemporary evidence. This list of medicines may be compiled from appropriate national or international guidelines, local formularies and knowledge of current practice.

Step 1.2. Medication history

A medication history is the part of a pharmaceutical consultation that identifies and documents allergies or other serious adverse medication events, as well as information about how medicines are taken currently and have been taken in the past. It is the starting point for medicines reconciliation and medication review.

Obtaining accurate and complete medication histories has been shown to have a positive effect on patient care and pharmacists have demonstrated that they can compile such histories with a high degree of precision and reliability as part of medicines reconciliation. The benefit to the patient is that prescribing errors of omission or transcription are identified and corrected early, reducing the risk of harm and improving care.

Discrepancies between the history recorded by the medical team and that which the pharmacist elicits fall into two categories: intentional (where the medical team has made a decision to alter the regimen) or unintentional (where a complete record was not obtained). Discrepancies should be clarified with the prescriber or referred to a more senior pharmacist. Box 1.5 lists the key components of a medication history.

Box 1.5 Key components of a medication history

1. Introduce yourself to the patient and explain the purpose of the consultation.
2. Identify any allergies or serious adverse reactions and record these on the prescription chart, care notes or patient medication record.
3. Ascertain information about prescribed and non-prescribed treatments from:
   - the patient's recall
   - medicines in the patient's possession
   - referral letter (usually from the patient's primary care doctor)
   - copy of prescriptions issued or a repeat prescription list
   - medical notes
   - contact with the appropriate community pharmacist or primary care doctor.
4. Ensure the following are recorded:
   - generic name of medicine (unless specific brand is required)
   - dose
   - frequency
   - duration of therapy.
5. Ensure items such as inhalers, eye drops, topical medicines, herbal and homeopathic remedies are included, as patients often do not consider these as medicines.
6. Ascertain the patient's medication-taking behaviour.
7. Consider practical issues such as swallowing difficulties, ability to read labels and written information, container preferences, ordering or supply problems.
8. Document the history in an appropriate format.
9. Note any discrepancies between this history and that recorded by other health care professionals.
10. Ascertain if these discrepancies are intentional (from patient, nursing staff, medical staff or medical notes).
11. Communicate non-intentional discrepancies to the prescriber.
12. Document any other important medication-related information in an appropriate manner, for example, implications of chronic renal failure, dialysis, long-term steroid treatment.

Step 2. Selecting the medicine

The issues to be tackled at this stage include clinical and cost-effective selection of a medicine in the context of individual patient care. The list of expected treatments generated at step 1 is now scrutinised for its appropriateness for the patient. This requires three separate types of interaction to be identified: drug–patient, drug–disease and drug–drug. The interactions should be prioritised in terms of likelihood of occurrence and the potential severity of outcome should they occur.

Step 2.1. Identify drug–patient interactions

Many medicines have contraindications or cautions to their use that relate to age groups or gender. Potential drug–patient interactions should be identified that may arise with any of the medicines that could be used to treat the current and pre-existing conditions. Types of drug–patient interactions may include allergy or previous ADR, the impact of abnormal renal or hepatic function or chronic heart failure on the systemic availability of some medicines, and patients' preferences for certain treatment options, formulations or routes of administration.

Step 2.2. Identify drug–disease interactions

A drug–disease interaction may occur when a medicine has the potential to make a pre-existing condition worse. Older people are particularly vulnerable due to the co-existence of several chronic diseases and exposure to polypharmacy. Prevention of drug–disease interactions requires an understanding of the pharmacodynamic properties of medicines and an appreciation of their contraindications.

Step 2.3. Drug–drug interactions

Medicines may affect the action of other medicines in a number of ways. Those with similar mechanisms of action may show an enhanced effect if used together whilst those with opposing actions may reduce each other's effectiveness.

Metabolism of one medicine can be affected by a second that acts as an inducer or inhibitor of the cytochrome P450 enzyme system.

The practitioner should be able to identify common drug interactions and recognise those medicines with increased risk of potential interaction, such as those with narrow therapeutic indices or involving hepatic P450 metabolic pathways. It is important to assess the clinical significance of drug interactions and consider the options for effective management.

The list of potential, evidence-based treatments should be reviewed for possible drug–patient, drug–disease and drug–drug interactions. The refined list can then be compared with the medicines that have been prescribed for the patient. The practitioner should explore any discrepancies to ensure the patient does not experience an MRP. This may necessitate consultation with medical staff or other health care professionals, or referral to a more senior pharmacist.

Step 3. Administering the medicine

Many factors influence the effect that a medicine has at its locus of action. These include the rate and extent of absorption, degree of plasma protein binding and volume of distribution, and the routes of metabolism or excretion. Factors affecting bioavailability may include the extent of absorption of the drug from the gastro-intestinal tract in relation to food and other medicines, or the amount adsorped onto intravenous infusion bags and giving sets when used to administer medicines parenterally.

The liver has extensive capacity for drug metabolism, even when damaged. Nevertheless, the degree of hepatic impairment should be assessed from liver function tests and related to potential changes in drug metabolism. This is particularly important for medicines that require activation by the liver (pro-drugs) or those whose main route of elimination is transformation into water-soluble metabolites.

Table 1.6 summarises the main pharmaceutical considerations for step 3. At this point, the practitioner needs to ensure the following tasks have been completed accurately.

Step 3.1. Calculating the appropriate dose

Where doses of oral medicines require calculation, this is usually a straightforward process based on the weight of the patient. However, medicines to be administered parenterally may require more complex calculations, including knowledge of displacement values (particularly for paediatric doses) and determination of appropriate concentrations in compatible fluids and rates of infusion.

Step 3.2. Selecting an appropriate regimen

Giving medicines via the oral route is the preferred method of administration. Parenteral routes carry significantly more risks, including infection associated with vascular access. This route, however, may be necessary when no oral formulation exists or when the oral access is either impossible or inappropriate because of the patient's condition.

Table 1.6 Pharmaceutical considerations in the administration of medicines

Dose	Is the dose appropriate, including adjustments for particular routes or formulations? Examples: differences in dose between intravenous and oral metronidazole, intramuscular and oral chlorpromazine, and digoxin tablets compared with the elixir
Route	Is the prescribed route available (is the patient nil by mouth?) and appropriate for the patient? Examples: unnecessary prescription of an intravenous medicine when the patient can swallow, or the use of a solid dosage form when the patient has dysphagia
Dosage form	Is the medicine available in a suitable form for administration via the prescribed route?
Documentation	Is documentation complete? Do nurses or carers require specific information to administer the medicine safely? Examples: appropriateness of crushing tablets for administration via nasogastric tubes, dilution requirements for medicines given parenterally, rates of administration and compatibilities in parenteral solutions (including syringe drivers)
Devices	Are devices required, such as spacers for inhalers?

Although simple regimens (once- or twice-daily administration) may facilitate adherence, some medicines possess short half-lives and may need to be given more frequently. The practitioner should be familiar with the duration of action of regularly encountered medicines to ensure dosage regimens are designed optimally.

Step 4. Providing the medicine

Ensuring that a prescription is legal, legible, accurate and unambiguous contributes in large measure to the right patient receiving the right medicine at the right time. For the majority of pharmacists this involves screening prescriptions written by other professionals, but those acting as supplementary and independent prescribers need to be cognisant of guidance on prescribing, such as that contained within the British National Formulary, when generating their prescriptions.

In providing a medicine for an individual, due account must be taken of the factors that influence the continued availability and supply of the medicine within the hospital or community setting, for example, formulary and drug tariff status, primary/secondary shared care arrangements, and whether the prescribed indication is within the product licence. This is particularly important with unlicensed or non-formulary medicines when information and agreement

on continuation of prescribing, recommended monitoring and availability of supply are transferred from a hospital to primary care setting.

Risks in the dispensing process are reduced by attention to products with similar names or packaging, patients with similar names, and when supplying several family members at the same time. Medicines should be labelled accurately, with clear dosage instructions and advisory labels, and presented appropriately for patients with specific needs, for example, the visually impaired, those unable to read English or with limited dexterity.

Step 5. Monitoring therapy

Monitoring criteria for the effectiveness of treatment and its potential adverse effects can be drawn from the characteristics of the prescribed medicines used or related to specific patient needs. Close monitoring is required for medicines with narrow therapeutic indices and for the subset of drugs where therapeutic drug monitoring may be beneficial, for example, digoxin, phenytoin, theophylline and aminoglycosides. Anticoagulant therapy, including warfarin and unfractionated heparin, is associated with much preventable medication-related morbidity and always warrants close scrutiny.

Throughout this textbook, details are presented on the monitoring criteria that may be used for a wide range of medicines. Patients with renal or hepatic impairment or an unstable clinical condition need particular attention because of the likely requirement for dosage adjustment or change in therapy.

Step 6. Patient advice and education

There is a vast quantity of information on drug therapy available to patients. The practitioner's contribution in this context is to provide accurate and reliable information in a manner that the patient can understand. This may require the pharmacist to convey the benefits and risks of therapy, as well as the consequences of not taking medicines.

Information about medicines is best provided at the time of, or as soon as possible after, the prescribing decision. In the hospital setting, this means enabling patients to access information throughout their stay, rather than waiting until discharge. With many pharmacy departments providing medicines in patient packs, the patient can be alerted to the presence of information leaflets, encouraged to read them and ask any questions they may have. This approach enables the patient to identify their own information needs and ensures the pharmacist does not create a mismatch between their own agenda and that of the patient. However, there will be a need to explain clearly the limitations of leaflets, particularly when medicines are prescribed for unlicensed indications.

Although the research on adherence indicates the primacy of information that has been tailored to the individual's needs, resources produced by national organisations, such as Diabetes UK (www.diabetes.org.uk) and British Heart Foundation (www.bhf.org.uk), may also be of help to the patient and their family or carers. In addition, patients often require specific information to support their daily routine of taking medicines. All written information, including medicines reminder charts, should be dated and include contact details of the pharmacist to encourage patients to raise further queries or seek clarification.

Step 7. Evaluating effectiveness

The provision of drug therapy for the purpose of achieving definite outcomes is a fundamental objective of pharmaceutical care. These outcomes need to be identified at the outset and form the basis for evaluating the response to treatment. Practitioners delivering pharmaceutical care have a responsibility to evaluate the effectiveness of therapy by reviewing steps 1–6 above and taking appropriate action to ensure the desired outcomes are achieved. Depending on the duration of direct engagement with a patient's care, this may be a responsibility the pharmacist can discharge in person or it may necessitate transfer of care to a colleague in a different setting where outcomes can be assessed more appropriately.

Case study

The following case is provided to illustrate the application of several steps in the delivery of pharmaceutical care. It is not intended to be a yardstick against which patient care should be judged.

Case 1.1

Mr JB, a 67-year-old retired plumber, has recently moved to your area and has come to the pharmacy to collect his first prescription. He has a PMH of coronary heart disease (CHD) and has recently had a coronary artery stent inserted. He has a long history of asthma which is well controlled with inhaled medicines.

Step 1. Establishing the need for drug therapy

What classes of medicines would you expect to be prescribed for these indications?

Mr JB gives a complete medication history that indicates he takes his medicines as prescribed, he has no medication-related allergies, but does suffer from dyspepsia associated with acute use of non-steroidal anti-inflammatory agents. He has a summary of his stent procedure from the hospital that indicates normal blood chemistry and liver function tests.

Step 2. Selecting the medicine

What drug–patient, drug–disease and drug–drug interactions can be anticipated (Table 1.7).

Steps 3 and 4. Administering and providing the medicines

What regimen and individualised doses would you recommend for Mr JB (Table 1.8).

Table 1.7 The case of Mr JB: potential drug interactions with the patient, the disease or other drugs

	Drug–patient interactions	Drug–disease interactions	Drug–drug interactions
Medicines that should be prescribed for CHD			
Aspirin	Previous history of dyspepsia	Aspirin should be used with caution in asthma	Combination of antiplatelet agents increases risk of bleeding
Clopidogrel	Previous history of dyspepsia		
Statins			Possible increased risk of myopathy if simvastatin given with diltiazem
β-Blockers		β-Blocker contraindicated in asthma	Combination of different agents to control angina may lead to hypotension
Diltiazem			Reduces metabolism of simvastatin thereby increasing the risk of side effects
Nitrates (GTN spray)	Previous history of side effects (e.g. headache, flushing) may result in patient not using spray when required		
Medicines that may be prescribed for asthma			
β2-Agonist inhalers	Patient's ability to use inhaler devices effectively	β2-Agonists can cause tachycardia	
Steroid inhalers			
Antimuscarinic inhalers		Antimuscarinic agents can cause tachycardia and atrial fibrillation	Antimuscarinics may reduce effect of sublingual nitrate tablets (failure to dissolve under tongue owing to dry mouth)

CHD, coronary heart disease.

Table 1.8 The case of Mr JB: possible therapeutic regimen

	Recommendation	Rationale
Medicines that should be prescribed for CHD		
Aspirin	75 mg daily orally after food	Benefit outweighs risk if used with PPI
Clopidogrel	75 mg daily orally after food	Benefit outweighs risk if used with PPI Length of course should be established in relation to previous stent
Lansoprazole	15 mg daily orally	Decreases risk of GI bleeds with combination antiplatelets Concerns about some PPIs reducing the effectiveness of clopidogrel makes selection of specific PPI important
Simvastatin	20 mg daily orally	Low dose selected due to diltiazem reducing the metabolism of simvastatin and increasing the risk of side effect
Nitrates	2 puffs sprayed under the tongue when required for chest pain	

Continued

This predicted regimen can be compared with the prescribed therapy and any discrepancies resolved with the prescriber. Step 4 (provision) in Mr JB's case would be relatively straightforward.

Steps 5, 6 and 7. Monitoring therapy, patient education and evaluation

What criteria would you select to monitor Mr JB's therapy and what information would you share with the patient? What indicators would convey effective management of his condition (Table 1.9).

Quality assurance of clinical practice

Quality assurance of clinical pharmacy has tended to focus on the review of performance indicators, such as intervention rates, or rely upon experienced pharmacists to observe and comment on the practice of others using local measures. The lack of generally agreed or national criteria raises questions about the consistency of these assessments, where they take place, and the overall standard of care provided to patients. Following the Bristol Royal Infirmary Inquiry (2001) into

Table 1.8 The case of Mr JB: possible therapeutic regimen—cont'd

	Recommendation	Rationale
Diltiazem	90 mg m/r twice a day	Used for rate control as β-blockers contraindicated in asthma
Ramipril	10 mg daily	To reduce the progression of CHD and heart failure
Medicines that may have been prescribed		
Salbutamol inhaler	2 puffs (200 µcg) to be inhaled when required	Patient should follow asthma treatment plan if peak flow decreases
Beclometasone inhalers	2 puffs (400 µcg) twice a day	Asthma treatment plan which may include increasing the dose of inhaled steroids if peak flow decreases

CHD, coronary heart disease; PPI, proton pump inhibitor; GI, gastro-intestinal; m/r, modified release.

Table 1.9 The case of Mr JB: monitoring criteria and patient advice

	Recommendation
Drugs that should be prescribed for CHD	
Aspirin	Ask patient about any symptoms of dyspepsia or worsening asthma
Clopidogrel	Ask patient about any symptoms of dyspepsia
Lansoprazole	If PPIs don't resolve symptoms, primary care doctor should be consulted
Simvastatin	Liver function tests 3 months after any change in dose, or annually Creatine kinase only if presenting with symptoms of unexplained muscle pain Cholesterol levels 3 months after any change in dose, or annually if at target
Nitrates (GTN spray)	Frequency of use to be noted. Increasing frequency that results in a resolution of chest pain should be reported to primary care doctor and anti-anginal therapy may be increased ANY use that does not result in resolution of chest pain requires urgent medical attention
Diltiazem	Blood pressure and pulse monitored regularly
Ramipril	Renal function and blood pressure monitored within 2 weeks of any dose change, or annually
Drugs that may have been prescribed for asthma	
Salbutamol inhaler	Salbutamol use should be monitored as any increase in requirements may require increase in steroid dose
Beclometasone inhalers	Monitor for oral candidiasis

paediatric cardiac surgery, there has been much greater emphasis on the need for regulation to maintain the competence of health care professionals, the importance of periodic performance appraisal coupled with continuing professional development, and the introduction of revalidation.

The challenges for pharmacists are twofold: first, to demonstrate their capabilities in a range of clinical pharmacy functions and second, to engage with continuing professional development in a meaningful way to satisfy the expectations of pharmaceutical care and maintain registration with, for example, the General Pharmaceutical Council in the UK. The pragmatic approach to practice and the clinical pharmacy process outlined throughout this chapter has been incorporated into a professional development framework, called the General Level Framework (GLF) available at: www.codeg.org, that can be used to develop skills, knowledge and other attributes irrespective of the setting of the pharmacist and their patients.

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2 Prescribing

H. Marlow and C. Whittlesea

Key points

- Prescribers need to assess and manage the potential benefits and harms of treatment.
- Patients should receive cost-effective medication appropriate to their clinical needs, in doses that meet their requirements and for an adequate period of time.
- Respect for patient autonomy, obtaining consent and sharing decision making is a fundamental part of the prescribing process.
- The consultation is a fundamental part of clinical practice and requires effective interpersonal reasoning and practical skills.
- Using a consultation framework is recommended to ensure relevant issues are covered.
- Prescribing is a complex mix of factors - evidence, external influences and cognitive biases - and these should be recognised.

To prescribe is to authorise by means of a written prescription the supply of a medicine. Prescribing incorporates the processes involved in decision making undertaken by the prescriber before the act of writing a prescription. Historically, prescribing has been the preserve of those professionals with a medical, dental or veterinary training. As the role of other health care professionals such as pharmacists and nurses has expanded, prescribing rights have in turn been extended to them. The premise for this development has been that it better utilises the training of these professional groups, is clinically appropriate and improves patient access.

Regardless of the professional background of the individual prescriber, the factors that motivate them to prescribe a particular medicine are a complex mix of evidence of effectiveness and harm, external influences and cognitive biases. A rational approach to prescribing uses evidence and has outcome goals and evaluates alternatives in partnership with the patient. With the advent of new professional groups of prescribers (non-medical prescribers), it is increasingly important to understand the components of rational and effective prescribing, and the influences on this process. There is a need for a systematic approach to prescribing, and an understanding of the factors that influence the decision to prescribe a medicine. These issues will be covered in the following sections. Initially, the fundamentals of rational and effective prescribing will be discussed, followed by a brief outline of the acquisition of prescribing rights by pharmacists and the associated legal framework. The final section will cover the prescribing process and the factors that influence this.

Rational and effective prescribing

Prescribing a medicine is one of the most common interventions in health care used to treat patients. Medicines have the potential to save lives and improve the quality of life, but they also have the potential to cause harm, which can sometimes be catastrophic. Therefore, prescribing of medicines needs to be rational and effective in order to maximise benefit and minimise harm. This is best done using a systematic process that puts the patient at the heart of the process (Fig. 2.1).

What is meant by rational and effective prescribing?

There is no universally agreed definition of good prescribing. The WHO promotes the rational use of medicines, which requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. However, a more widely used framework for good prescribing has been described (Barber, 1995) and identifies what the prescriber should be trying to achieve, both at the time of prescribing and in monitoring treatment thereafter. The prescriber should have the following four aims:

- Maximise effectiveness
- Minimise risks
- Minimise costs
- Respect the patient's choices.

This model links to the four key principles of biomedical ethics: beneficence, non-maleficence, justice and veracity, and respect for autonomy, and can be applied to decision making at both an individual patient level and when making decisions about medicines for a wider population, for example in a Drug and Therapeutics Committee. One of the strengths of this model is the consideration of the patient's perspective and the recognition of the inherent tensions between the four key aims.

Another popular framework to support rational prescribing decisions is known as STEPS (Preskorn, 1994). The STEPS

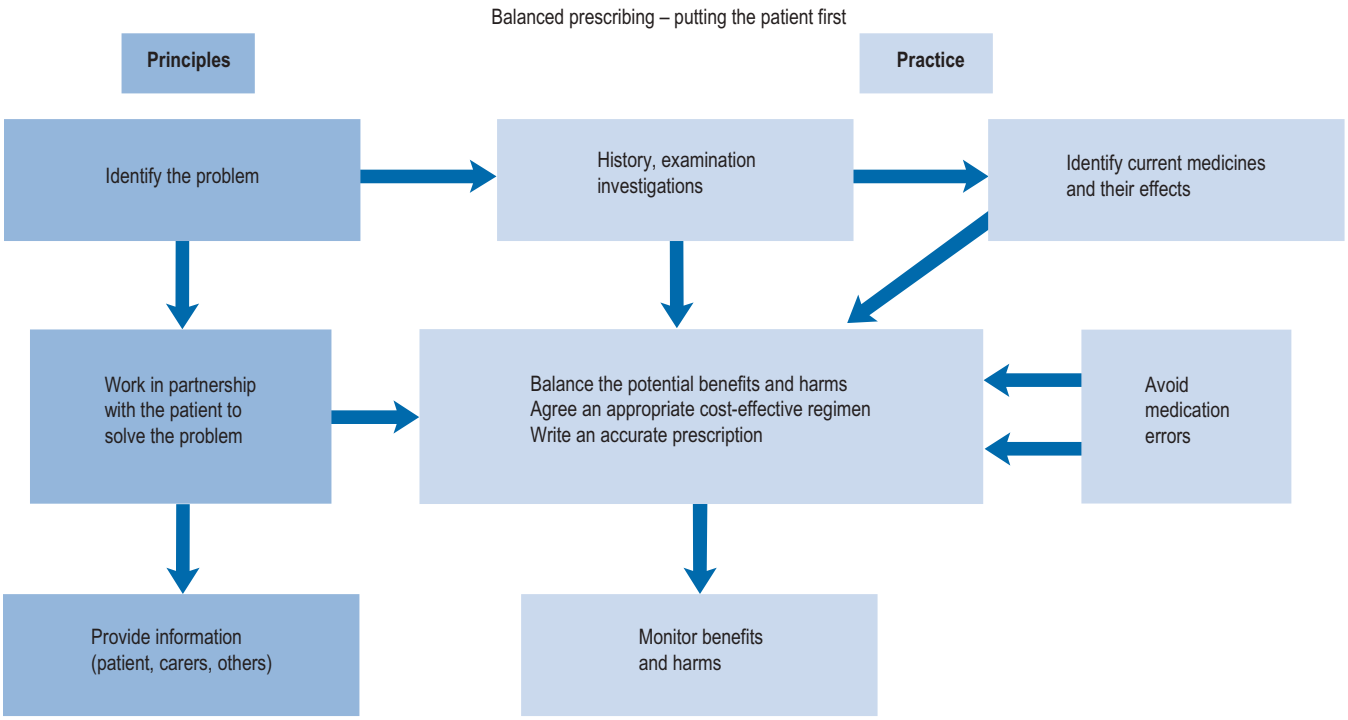

Fig. 2.1 A framework for good prescribing (from Background Briefing. A blueprint for safer prescribing 2009 © Reproduced by permission of the British Pharmacological Society.)

model includes five criteria to consider when deciding on the choice of treatment:

- Safety
- Tolerability
- Effectiveness
- Price
- Simplicity.

Inappropriate or irrational prescribing

Good prescribing is sometimes defined as the lack of irrational prescribing. Prescribing can be described as irrational for many reasons:

- Poor choice of a medicine
- Polypharmacy or co-prescribing of interacting medicine
- Prescribing for a self-limiting condition
- Continuing to prescribe for a longer period than necessary
- Prescribing too low a dose of a medicine
- Prescribing without taking account of the patient's wishes.

Inappropriate or irrational prescribing can result in serious morbidity and mortality, particularly when childhood infections or chronic diseases such as hypertension, diabetes, epilepsy and mental disorders are being treated. Inappropriate prescribing also represents a waste of resources and, as in the case of antimicrobials, may harm the health of the public by contributing to increased antimicrobial resistance. Finally, an over-willingness to prescribe stimulates inappropriate patient demand and fails to help the patient understand when they should seek out support from a health care professional.

Pharmacists as prescribers and the legal framework

Evolution of non-medical prescribing

Independent prescribing is defined as 'prescribing by a practitioner (doctor, dentist, nurse, pharmacist) who is responsible and accountable for the assessment of patients with undiagnosed or diagnosed conditions and for decisions about the clinic management required including prescribing' (DH, 2006).

In 1986, a report was published in the UK ('Cumberlage report') which recommended that community nurses should be given authority to prescribe a limited number of medicines as part of their role in patient care (Department of Health and Social Security, 1986). Up to this point, prescribing in the UK had been the sole domain of doctors, dentists and veterinarians. This was followed in 1989 by a further report (the first Crown report) which recommended that community nurses should prescribe from a limited formulary (DH, 1989). The legislation to permit this was passed in 1992.

At the end of the 1990s, in line with the then UK government's desire to widen access to medicines by giving patients quicker access to medicines, improving access to service and making better use of the skills of health care professionals, the role of prescriber was proposed for other health care professionals. This change in prescribing to include non-medical prescribers (pharmacists, nurses and optometrists) was developed following a further review (Crown, 1999).

This report suggested the introduction of supplementary prescribers, that is, non-medical health professionals who could prescribe after a diagnosis had been made and a clinical management plan drawn up for the patient by a doctor (Crown, 1999).

Supplementary prescribing

The Health and Social Care Act 2001 allowed pharmacists and other health care professionals to prescribe. Following this legislation, in 2003, the Department of Health outlined the implementation guide allowing pharmacists and nurses to qualify as supplementary prescribers (DH, 2003). In 2005, supplementary prescribing was extended to physiotherapists, chiropodists/podiatrists, radiographers and optometrists (DH, 2005).

Supplementary prescribing is defined as a voluntary prescribing partnership between an independent prescriber (doctor or dentist) and a supplementary prescriber (nurse, pharmacist, chiropodists/podiatrists, physiotherapists, radiographers and optometrists) to implement an agreed patient-specific clinical management plan with the patient's agreement. This prescribing arrangement also requires information to be shared and recorded in a common patient file. In this form of prescribing the independent prescriber, that is the doctor or if appropriate the dentist, undertakes the initial assessment of the patient, determines the diagnosis and the initial treatment plan. The elements of this patient-specific plan, which are the responsibility of the supplementary prescriber, are then documented in the patient-specific clinical management plan. The legal requirements for which are detailed in Box 2.1. Supplementary prescribers can prescribe Controlled Drugs and also both off-label and unlicensed medicines.

Box 2.1 Overview of the requirements for a clinical management plan for supplementary prescribing

Legal requirements

Patient details
- Name of the patient to whom the plan relates
- Patient allergies
- Difficulties patient has with medicines

Disease and treatment
- Condition
- Class or name of medicines
- Limitations on doses, strength or time of treatment
- When to seek advice from, or refer back to independent prescriber
- Arrangements for notification of adverse drug reactions or incidents

Prescriber information
- Name of independent prescriber (doctor or dentist)
- Name of supplementary prescriber (pharmacist, nurse, physiotherapists, chiropodists/podiatrists, radiographers and optometrists)
- Start date
- Review date

Non-medical independent prescribing

Following publication of a report on the implementation of nurse and pharmacist independent prescribing within the NHS in England (DH, 2006), pharmacists were enabled to become independent prescribers as defined under the Medicines and Human Use (Prescribing; Miscellaneous Amendments) Order of May 2006. Pharmacist independent prescribers were able to prescribe any licensed medicine for any medical condition within their competence except Controlled Drugs and unlicensed medicines. The restriction on Controlled Drugs included those in Schedule 5 (CD Inv.POM and CD Inv.P) such as co-codamol. At the same time, nurses could also become qualified as independent prescribers (formerly known as Extended Formulary Nurse Prescribers) and prescribe any licensed medicine for any medical condition within their competence, including some Controlled Drugs. Since 2008, optometrists can also qualify as independent prescribers to prescribe for eye conditions and the surrounding tissue. They cannot prescribe for parenteral administration and they are unable to prescribe Controlled Drugs.

Following a change in legislation in 2010, pharmacist and nurse, non-medical prescribers, were allowed to prescribe unlicensed medicines (DH, 2010).

From the above it should be evident that in the UK suitably qualified pharmacists can prescribe as either supplementary or independent prescribers.

Accountability

Prescribers have the authority to make prescribing decisions for which they are accountable both legally and professionally. Accountability when prescribing covers three aspects – the law, the statutory professional body and the employer.

The law of Tort, the concept of a 'civil wrong', includes clinical negligence. In such a claim, the patient needs to demonstrate that the prescriber caused them injury or damage. For this allegation to be substantiated the patient needs to prove that the prescriber owed them a duty of care, that this duty of care was breached and that this caused the injury identified, and also that the injury was foreseeable. The law of Tort also permits actions for breach of confidentiality and also for battery, should a patient be treated without consent. Therefore, prescribers (independent and supplementary) are legally and professionally accountable for their decisions. This includes decisions not to prescribe and also ensuring that the prescription is administered as directed. The legal responsibility for prescribing always lies with the individual who signed the prescription. In addition, prescribers also have a responsibility to ensure the instructions are clear and not open to misinterpretation.

If a prescriber is an employee then the employer expects the prescriber to work within the terms of his/her contract, competency and within the rules/policies, standard operating procedure and guidelines, etc. laid down by the organisation. Therefore, working as a prescriber, under these conditions, ensures that the employer has vicarious liability. So should any patient be harmed through the action of the prescriber

and he/she is found in a civil court to be negligent, then under these circumstances the employer is responsible for any compensation to the patient. Therefore, it is important to always work within these frameworks, as working outside these requirements makes the prescriber personally liable for such compensation. To reinforce this message it has been stated that the job descriptions of non-medical prescribers should incorporate a clear statement that prescribing forms part of the duties of their post (DH, 2006).

Ethical framework

Four main ethical principles of biomedical ethics have been set out for use by health care staff in patient–practitioner relationships (Beauchamp and Childress, 2001). These principles are respect for autonomy, non-maleficence, beneficence, justice and veracity and need to be considered at all points in the prescribing process.

Autonomy

Autonomy recognises an individual patient's right to self-determination in making judgements and decisions for themselves and encompasses informed patient consent. Respect for autonomy is therefore a form of personal liberty which freely permits patients to choose whether they wish to have treatment in accordance with their own plans.

Confidentiality. Confidentiality is a fundamental right with respect to patient autonomy. Therefore, patients have the right to confidentiality, and consent is required to disclose information regarding their health and treatment.

Consent. Obtaining consent from a patient for treatment can be divided into three components: voluntariness, information and competency. Consent is invalid when it is given under pressure or coercion. Therefore, it is important that consent is obtained for each act and not assumed because this is a routine assessment or procedure and therefore can be carried out automatically. It is essential the patient understands their diagnosis, the benefit and rationale of the proposed treatment and the likelihood of its success together with the associated risks and consequences, for example side effects. Therefore, a prescriber needs to discuss these aspects with the patient. In addition, potential alternative treatments should also be discussed to allow the patient to make a comparison with the proposed plan. The prognosis if no treatment is prescribed should also be discussed. Such a wide-ranging discussion may require more than one appointment and reinforces the necessity for an ongoing patient–professional relationship focused on the needs of the patient. Associated with this is the need to determine if the patient has the competency to make decisions for themselves with respect to vulnerable groups such as those who have learning disabilities, children and the elderly. Young people aged 16 and 17 are normally presumed to be able to consent to their own treatment.

Gillick competence is used to determine if children have the capacity to make health care decisions for themselves. Children under 16 years of age can give consent as long as they can satisfy the prescriber that they have capacity to make this decision. However, with the child's consent, it is a good practice to involve the parents in the decision-making process. In addition, children under 16 may have the capacity to make some decisions relating to their treatment, but not others. So it is important that an assessment of capacity is made related to each decision. There is some confusion regarding the naming of the test used to objectively assess legal capacity to consent to treatment in children under 16, with some organisations and individuals referring to Fraser guidance and others Gillick competence. Gillick competence is the principle used to assess the capacity of children under 16, while the Fraser guidance refers specifically to contraception (Wheeler, 2006).

The Mental Capacity Act (2005) protects the rights of adults who are unable to make decisions for themselves. The fundamental concepts within this act are the presumption that every adult has capability and should be supported to make their own individual decision. The five key principles are listed in Box 2.2. Therefore, any decision made on their behalf should be as unrestrictive as possible and must be in the patient's own interest, not biased by any other individual or organisation's benefit. Advice regarding patient consent is listed in Box 2.3.

Non-maleficence

At the heart of the principle of non-maleficence is the concept of not knowingly causing harm to the patient. The principle is expressed in the Hippocratic Oath. This obligation not to harm is distinct from the obligation to help others. While

Box 2.2 Overview of the five principles of the Mental Capacity Act

- A person is assumed to have capacity unless it is established that he/she lacks capacity.
- A person should not be treated as unable to make a decision unless all practical steps to enable him/her to do this have been taken without success.
- A person cannot be treated as unable to make a decision because he/she makes an unwise decision.
- Acts or decisions made for or on behalf of a person who lacks capacity must be in that person's best interests.
- Before an act or decision is made, the purpose has to be reviewed to assess if it can be achieved as effectively in a way that is less restrictive of the person's rights/freedom of action.

Box 2.3 Advice on patient consent

- Take care when obtaining consent.
- Give the patient understandable information about all significant possible adverse outcomes.
- Ensure the patient has the opportunity to ask questions/consider his/her options.
- Document the advice/warnings provided in the patient's notes.
- Invite the patient to sign to say that he/she understands, and accepts the risks explained.
- Record in the patient's notes if they decline to undergo a treatment/procedure.

codes of all health care professionals outline obligations not to harm clients, many interventions result in some harm, however transitory. Sometimes one act can be described as having a 'double effect', that is, two possible effects: one good effect (intended) and one harmful effect (unintended). The harmful effect is allowed if proportionally it is less than the good effect. Therefore, it is important for prescribers to review both the potential positive effects of treatment, for example symptom control, and the negative effects, for example side effects. It is also important to consider both acts of commission and omission, as a failure to prescribe can also cause harm to the patient.

Beneficence

This is the principle of doing good and refers to the obligation to act for the benefit of others that is set out in codes of professional conduct, for example, pharmacists' code of ethics and professional standards and guidance (Royal Pharmaceutical Society of Great Britain, 2009). Beneficence is referred to both physical and psychological benefits of actions and also related to acts of both commission and omission. Standards set for professionals by their regulatory bodies such as the General Pharmaceutical Council can be higher than those required by law. Therefore, in cases of negligence the standard applied is often that set by the relevant statutory body for its members.

Justice and veracity

This last principle is related to the distribution of resources to ensure that such division or allocation is governed by equity and fairness. This is often linked to cost-effectiveness of treatment and potential inequalities if treatment options are not offered to a group of patients or an individual. However, as a prescriber it is important to consider the evidence base for the prescribed medicine and also to review the patient as an individual to ensure the treatment offered adheres to this principle. This principle of fairness and freedom from discrimination therefore encompasses Human Rights including the need for assessment of medication as part of the Disability Discrimination Act. Health care professionals have a duty under this act to make reasonable adjustments to ensure that all patients have the same opportunity for good health. Therefore, a prescriber should also assess with the patient that the medication prescribed can be accessed by them. Veracity or 'truth telling' underpins both effective communication and patient consent.

Professional frameworks for prescribing

Each professional regulatory body has standards to which their members must adhere. Members are accountable to such bodies for their practice and can be sanctioned by these bodies if their actions do not adhere to these standards. Therefore, individuals will be held accountable by their respective statutory body for their prescribing decisions.

The professional standards for pharmacists are defined within 'Medicines, Ethics and Practice' and contain additional requirements for pharmacists who are qualified as non-medical prescribers and also good practice guidance (Royal Pharmaceutical Society of Great Britain, 2009). This guidance provides advice on a wide range of areas including self-audit, promotions, gifts from drug companies, written agreement with the employing organisation describing the prescriber's scope of practice, liability and indemnity arrangements, competency to prescribe and not just prescribing and dispensing a medicine.

Off-label and unlicensed prescribing

For a medicine to be licensed for use in a specific country, the manufacturer must obtain a marketing authorisation, formerly called the product license. This details the patients, conditions and purpose under which the medicine is licensed for use. Any medicine which does not have a marketing authorisation for the specific country where it is prescribed is termed 'unlicensed'. Unlicensed medicines prescribed include new medicines undergoing clinical trial, those licensed and imported from another country but not licensed in the country where they are to be used. It also includes 'specials' manufactured to meet a specific patient's needs or produced when two licensed medicines are mixed for administration.

However, if a licensed medicine is prescribed outside that specified in the marketing authorisation then this is described as 'off-label'. This happens in practice, for example many medicines are not licensed for use in children but are prescribed for them. In addition, some established medicines are prescribed for conditions outside their marketing authorisation, for example amitriptyline for neuropathic pain and azathioprine in Crohn's disease. The British National Formulary includes information on off-label use as an annotation of 'unlicensed indication' to inform health care professionals. The details of a medicine's marketing authorisation are provided in the Summary of Product Characteristics.

The company which holds the marketing authorisation has the responsibility to compensate patients who are proven to have suffered unexpected harm caused by the medicine when prescribed and used in accordance with the marketing authorisation. Therefore, if a medicine is prescribed which is either unlicensed or off-label, the prescriber carries professional, clinical and legal responsibility and is therefore liable for any harm caused. Best practice on the use of unlicensed and off-label medicines is described in Box 2.4. In addition, all health care professionals have a responsibility to monitor the safety of medicines. Suspected adverse drug reactions should therefore be reported in accordance with the relevant reporting criteria.

Prescribing across the interface between primary and secondary care

When a patient moves between care settings, there is a risk that a 'gap' in care will take place. These 'gaps' in care are almost always as a result of poor communication and frequently involve medicines, particularly when the patient is

Box 2.4 Advice for prescribing unlicensed and off-label medicines (from Drug Safety Update, 2009; 2: 7, with kind permission from MHRA)

Consider

- Before prescribing an unlicensed medicine be satisfied that an alternative licensed medicine would not meet the patient's needs.
- Before prescribing an off-label medicine be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative.
- Before prescribing an unlicensed medicine or using an off-label medicine:
  - be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy;
  - take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring and follow up;
  - record the medicine prescribed and, where common practice is not being followed, the reason for prescribing the medicine; you may wish to record that you have discussed this with the patient.

Communicate

- You give patients, or those authorising treatment on their behalf, sufficient information about the proposed treatment, including known serious or common adverse drug reactions, to enable them to make an informed decision.
- Where current practice supports the use of a medicine outside the terms of its license, it may not be necessary to draw attention to the license when seeking consent. However, it is a good practice to give as much information as patients or carers require or which they see as relevant.
- You explain the reasons for prescribing an off-label medicine or prescribing an unlicensed medicine where there is little evidence to support its use, or where the use of the medicine is innovative.

discharged from hospital into a community setting. So far, there is no evidence-based solution to these problems. The primary care prescriber with the responsibility for the continuing management of the patient in the community may be required to prescribe medicines with which they are not familiar. The prescriber should be fully informed and competent to prescribe a particular medicine for his/her patient. Supporting information from the hospital, in the form of shared care guidelines, can help inform the prescriber about medicines with which they may not be very familiar. Overall, the decision about who should take responsibility for continuing care or prescribing treatment after the initial diagnosis or assessment should be based on the patient's best interests rather than on the health care professional's convenience or the cost of the medicine. However, it is legitimate for a prescriber to refuse to prescribe where they consider they have insufficient expertise to accept responsibility for the prescription or where the product is of a very specialised nature and/or requires complex ongoing monitoring. Professional bodies are developing principles for communication between health care professionals in primary and secondary care to improve patient safety.

Clinical governance

Clinical governance is defined as 'the system through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care, by creating an environment in which clinical excellence will flourish' (DH, 1998). It is a process embraced by the NHS to ensure that the quality of health care embedded within organisations is continuously monitored and improved. Clinical governance parallels corporate governance within commercial organisations and as such provides a systematic set of mechanisms such as duties, accountabilities and rules of conduct to deliver quality health care.

Clinical governance is described as having seven pillars:

- Patient, service user, carer and public involvement
- Risk management
- Clinical audit
- Staffing and management
- Education, training and continuing professional development (CPD)
- Research and clinical effectiveness
- Use of information.

Within the NHS, standards of practice have been developed and monitored to ensure risks are managed and controlled. As part of this framework the performance of staff is also assessed and remedial action taken, if required. NHS organisations have clinical governance requirements for their staff which include requirements for non-medical prescribing.

Professional bodies have also incorporated clinical governance into their codes of practice. The four tenants of clinical governance are to ensure clear lines of responsibility and accountability; a comprehensive strategy for continuous quality improvement; policies and procedures for assessing and managing risks; procedures to identify and rectify poor performance in staff. Therefore, the professional bodies such as those of pharmacists, nurses and optometrists have also identified clinical governance frameworks for independent prescribing as part of their professional codes of conduct. The General Pharmaceutical Council, the UK pharmacy regulator, code of practice provided a framework not only for the individual pharmacist, non-medical prescriber, but also for their employing organisation. Suggested indicators for good practice are detailed in Box 2.5.

Competence and competency frameworks

Competence can be described as the knowledge, skills and attributes required to undertake an activity to a specific minimum standard within a defined environment. A competency framework is a group of competencies identified as essential to effectively perform a specific task. It can be used by an individual or an organisation to assess performance in this defined area. For example, it can be used for staff selection/recruitment, training and performance review.

The National Prescribing Centre has published a competency framework for pharmacist prescribers

Box 2.5 Overview of clinical governance practice recommendations for prescribers

- Ensure effective communication with patients and carers to meet the patient's needs, so that the patient can make informed choices about their treatment.
- Prescribe within competence (scope of practice).
- Obtain patient consent for investigations and management.
- Document in the patient's medical record, a comprehensive record of the consultation and the agreed treatment plan.
- Undertake full assessment of patients competently and with consent.
- Prescribe safely, legally, appropriately, clinically and cost-effectively with reference to national and local guidelines.
- Assess and manage risk of treatment and associated investigations.
- Prescribe and refer in accordance with the clinical management plan if relevant.
- Ensure the secure storage of prescriptions and follow the relevant organisational procedures if they are lost or stolen.
- Ensure wherever possible separation of prescribing and dispensing; prescribing and administration.
- Audit prescribing practice.
- Identify and report incidents and adverse drug reactions.
- Participate in and record continuing professional development relating to prescribing.
- Follow organisational procedures for dealing with the pharmaceutical industry regarding gifts and hospitality.

(Granby and Picton, 2006) which is described in Table 2.1. This framework is composed of three areas: the consultation, prescribing effectively and prescribing in context. These three areas are further subdivided to provide nine competencies each with an overarching statement. The nine competencies are:

- Clinical and pharmaceutical knowledge
- Establishing options
- Communicating with patients
- Prescribing safety
- Prescribing professionally
- Improving prescribing practice
- Information in context
- The NHS in context (the principles apply to all health care organisations)
- The team and individual context.

Each of these competencies is supported by a series of statements/behavioural indicators, all of which an individual needs to demonstrate they have achieved the overall competency (Table 2.1). Prescribers can review their prescribing performance using the nine competencies and the associated 77 behavioural indicators using this framework as a self-assessment tool. The framework is particularly useful when structuring ongoing CPD.

Table 2.1 Overview of the National Prescribing Centre competency framework for pharmacists (Granby and Picton, 2006)

Competency area	Competency	Behaviour indicator
Consultation	Clinical and pharmaceutical knowledge	10 statements For example, understands the conditions being treated, their natural progress and how to assess their severity
	Establishing options	14 statements For example, assesses the clinical condition using appropriate techniques and equipment
	Communicating with patients	11 statements For example, explains the nature of the patient's condition, the rationale behind and potential risks and benefits of management options
Prescribing effectively	Prescribing safely	9 statements For example, only prescribes a medicine with adequate, up-to-date knowledge of its actions, indications, contraindications, interactions, cautions, dose and side effects
	Prescribing professionally	8 statements For example, accepts personal responsibility for own prescribing and understands the legal and ethical implications of doing so
	Improving prescribing practice	7 statements For example, reports prescribing errors and near misses, reviews practice to prevent recurrences
Prescribing in context	Information in context	6 statements For example, critically appraises the validity of information sources (e.g. promotional literature, research)
	The NHS in context	5 statements For example, follows relevant local and national guidance for medicines use (e.g. local formularies, care pathways, NICE guidance)
	The team and individual context	7 statements For example, establishes relationships with colleagues based on understanding, trust and respect for each other's roles

The prescribing process

Consultation

The consultation is a fundamental part of the prescribing process and the prescriber needs to understand and utilise this in order to help them practise effectively. The medical model of disease, diagnosis and prescribing is often central to practice, but an understanding of the patient's background together with their medical beliefs and anxieties is equally important in helping the prescribers understand their own role and behaviours alongside those of their patients. A broad range of practical skills are needed in the consultation:

- *Interpersonal skills:* the ability to communicate and make relationships with patients.
- *Reasoning skills:* the ability to gather appropriate information, interpret the information and then apply it both in diagnosis and management.
- *Practical skills:* the ability to perform physical examinations and use clinical instruments.

The style in which the consultation is undertaken is also important. The paternalistic prescriber–patient relationship is no longer appropriate. This has been replaced in modern health care by a more patient-centred focus that ensures patient autonomy and consent. This uses a task-orientated approach to keep consultation times to a reasonable duration and set parameters to ensure a realistic expectation from the consultation.

An example of this is the Calgary Cambridge framework which can be used to structure and guide patient consultations (Silverman et al., 2005). The framework is represented in Fig. 2.2. The five key stages of the consultation are:

- Initiating the session
- Gathering information
- Physical examination
- Explanation and planning
- Closing the session.

In addition to these stages there are two key tasks performed throughout the consultation. These are 'providing structure' and 'building the patient–prescriber relationship'. These two tasks are vital in ensuring an effective consultation. For a patient–prescriber communication to be effective, it is important that this focuses on interaction between the patient and the prescriber and is not just passive transmission of information. Feedback from the patient about the information received is essential for effective communication and will be covered in more detail below.

Building relationships

Non-verbal communication is important and can be used by the prescriber to gain information from the patient. Facial expressions and body posture can give clues about how the patient is feeling, for example anxious or tired. Proximity and

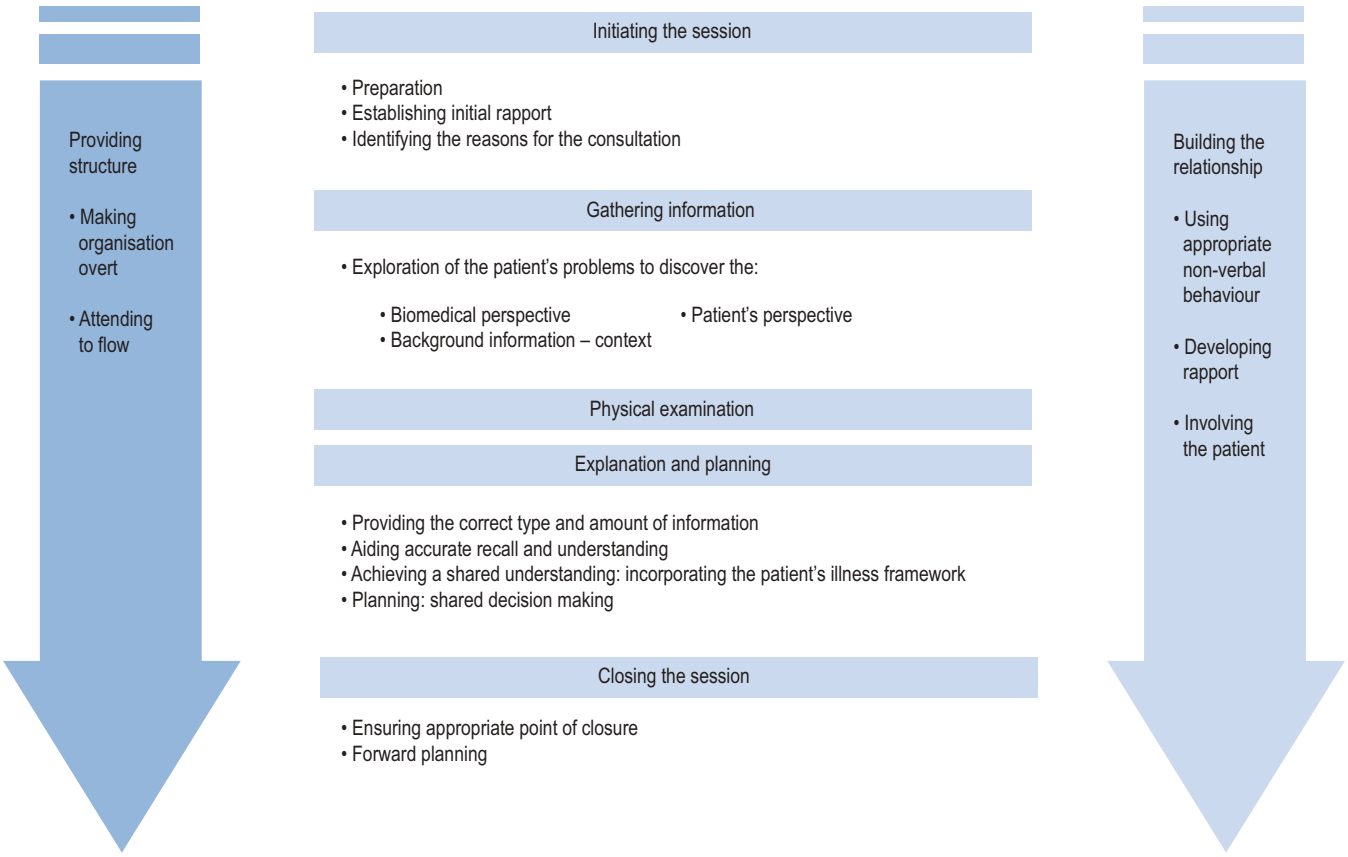

Fig. 2.2 Calgary Cambridge consultation framework (Silverman et al., 2005). Reproduced with kind permission from the Radcliffe Publishing Ltd, Oxford.

eye contact are also important to determine if the patient is activity engaged in the conversation or are they distracted. Such non-verbal clues, for example anxiety, tiredness and pain, can then be explored verbally with the patient.

The prescribers also need to review their own non-verbal communication to ensure this reinforces the verbal message they are giving to the patient. For example, doctors who face the patient, make eye contact and maintain an open posture were regarded by their patients to be more interested and empathic (Harrigan et al., 1985). Also health care professionals in primary care who demonstrated non-verbal intimacy (close distance, leaning forward, appropriate body orientation and touch) had increased patient satisfaction (Larsen and Smith, 1981).

As eye contact is an important non-verbal form of communication, obtaining information from patient records and documenting the consultation could undermine these skills. Therefore, it is important to read notes in advance of the consultation and avoid writing up the outcome while the patient is speaking. Indicating to the patient that references need to be made to their record or information documented ensures the patient is informed about the break in the consultation. This strategy should be adopted for both paper and computer-based records.

Developing rapport is also essential to building an effective patient–prescriber relationship. This can be achieved by providing an accepting response to the patient's concerns and expectations. This is achieved by acknowledging the patient's views and valuing their contribution and accepting this information in a non-judgemental way. This does not necessarily mean that the prescriber agrees with information but that they accept that this is a legitimate view from the patient's perspective. This can be reinforced by summarising the patient's view. The prescriber should acknowledge the patient's coping efforts and self-care. Avoiding jargon and explaining complex concepts in simple terms, to enable patients to understand the diagnosis and management, is also important.

Providing structure

This is important in the patient–prescriber consultation to enable the five key stages to be effectively completed. The prescriber needs to establish the boundaries for the consultation, that is, the time available and the topics covered and termination of the consultation. Therefore, as the power in the consultation is with the prescriber, it is his/her responsibility to guide the consultation and involve the patient. This is to ensure a patient-centred collaborative partnership is established. This can be achieved by using problem identification, screening and agenda-setting skills. The use of a logical sequence, signposting from one part of the consultation to the next and including an initial and end summary, will provide an effective structure to the consultation.

Initiating the session

During the first stage of the consultation the prescriber needs to greet the patient and confirm his/her identity. They should also ensure the environment for the consultation is appropriate for maintaining eye contact and ensuring confidentiality. The prescriber should also introduce him/herself, his/her role and gain relevant consent. During this stage the prescriber must demonstrate respect for the patient and establish a patient-centred focus. Using initially open and then closed questions the prescriber needs to identify the patient's problem/issues. By adopting this approach and actively listening, the prescriber is able to confirm the reason for the consultation and identify other issues. This allows the prescriber to negotiate an agenda for the next stages of the consultation through agreement with the patient and taking into account both the patient and prescriber's needs. This initial stage is vital for the success of the consultation as many patients have hidden agendas which, if not identified at this stage, can lead to these concerns not being addressed. Beckman and Frankel (1984) studied doctors' listening skills and identified that even minimal interruptions by doctors to initial patients' statements at the beginning of the consultation prevented patients' concerns from being expressed. This resulted in either these issues not being identified at all or they were raised by patient's late in the consultation

Gathering information

The aim of this stage is to explore the problem identified from both the patient and prescriber's perspective to gain background information which is both accurate and complete. Britten et al. (2000) identified that lack of patient participation in the consultation led to 14 categories of misunderstanding between the prescriber and patient. These included patient information unknown to the prescriber, conflicting information from the patient and communication failure with regard to the prescriber's decision. During this stage the illness framework, identified by exploring the patient's ideas, concerns, expectations and experience of his/her condition and effect on his/her life, is combined with the information gained by the prescriber through his/her biomedical perspective. This encompasses signs, symptoms, investigations and underlying pathology. Assimilation of this information leads the prescriber to a differential diagnosis. By incorporating information from both viewpoints, a comprehensive history detailing the sequence of events can be obtained using questioning, listening and clarification. This ends with an initial summary where the prescriber invites the patient to comment and contribute to the information gathered.

Physical examination

At the start of this stage it is important to again obtain the patient's consent for any examination by explaining the process and rationale for the assessment. The environment, for example room temperature and screening for the examination, is important and the prescriber should review this to ensure the patient's comfort.

Explanation and planning

This stage of the consultation incorporates three aspects: the differential diagnosis/hypothesis, the prescriber's management plan (investigations and alternative treatments), explanation and negotiating the plan of action with the patient.

In one UK study, doctors were found to overestimate the extent to which they completed the tasks of discussing the risk of medication, checking the ability of the patient to follow the treatment plan and obtaining the patient's input and view on the medication prescribed (Makoul et al., 1995).

In order to successfully accomplish this stage of the consultation, the prescriber needs to use a number of skills and also to involve the patient. The prescriber should ensure he/she gives the correct type and amount of information. This is done by assessing the patient's prior knowledge by employing both open and closed questions. By organising the information given into chunks which can be easily assimilated the prescriber can then check the patient understands the information given. Questioning the patient regarding additional information they require also helps to ensure the patient's involvement and maintains rapport. The prescriber must determine the appropriate time to give explanations and also allow the patient time to consider the information provided. Signposting can also be a useful technique to employ during this stage. Once again the language used should be concise, easy to understand and avoid jargon. Using diagrams, models and written information can enhance and reinforce patient understanding. The explanation should be organised into discreet sections with a logical sequence so that important information can be repeated and summarised. Box 2.6 summarises the issues the prescriber should consider before prescribing a medicine.

Box 2.6 Issues the prescriber should reflect upon before prescribing a medicine (National Prescribing Centre, 1998)

- What is the drug?
  - Is it novel?
  - Is it a line extension?
- What is the drug used for?
  - Licensed indications
  - Any restrictions on initiation
  - Does first line mean first choice?
- How effective is the drug?
  - Is there good evidence for efficacy?
  - How does it compare with existing drugs?
- How safe is the drug?
  - Are there published comparative safety data?
  - Has it been widely used in other countries?
  - Are the details contained in the Summary of Product Characteristics understood?
  - Are there clinically important drug interactions?
  - Are there monitoring requirements?
  - Can it be used long term?
- Who should not receive this drug?
  - Are there patients in whom it is contraindicated?
- Does the drug provide value for money?
  - Is there good evidence of cost-effectiveness compared to other available interventions?
  - What impact will this drug have on the health care budget?
- What is its place in therapy?
  - What advantages are there?
  - Are the benefits worth the cost?
  - Are there some patients that would particularly benefit?

To achieve shared understanding and shared decision making, it is important to incorporate the patient's perspective by relating the information given to the patient's illness framework. The patients also need to have the opportunity to ask questions, raise doubts and obtain clarification. This can be undertaken effectively by taking the patient's beliefs, culture, abilities and lifestyle into account when discussing treatment options, for example fasting during Ramadan, or use of memory aids to support adherence. The prescriber should also explain his/her rationale for the management plan identified and also discuss possible alternatives. By involving and negotiating with the patient in this way, a mutually acceptable treatment plan can be identified which allows the patient to take responsibility for his/her own health.

Closing the session

The effectiveness of the end of a consultation is as important as the preceding stages. A number of steps are undertaken during the closing stage. These include agreeing a contract with the patient as to the next steps to be taken by both patient and prescriber, for example additional investigations and/or referral. Safety net strategies are also employed and discussed, so the patient can identify unexpected outcomes or treatment failure and also understand who and how to contact the prescriber or another health care professional if appropriate. The end summary is an essential component of this stage and is used to briefly and accurately identify the management plan established during the previous stage in the consultation. This is followed by final checking that the patient has understood and consented to this management plan. At the end of the consultation the patient is given another opportunity to ask any final questions.

Communicating risks and benefits of treatment

Explaining the risks and benefits of treatment in an effective manner is an essential skill for health care professionals. This ensures patient's consent to treatment is informed and that the patient has an opportunity to participate in shared decision making about their treatment. Before this stage of the consultation is reached, the health care professional has to know the evidence about treatment, be able to apply it to the individual patient in front of them and then be able to communicate risks and benefits in terms the patient can understand.

It is important to communicate the risks and benefits of treatment in relation to medicines. This is because many medicines are used long term to treat or prevent chronic diseases, but we know they are often not taken as intended. Sometimes these medicines do not appear to have any appreciable beneficial effect on patients' symptoms, for example medicines to treat hypertension. Most patients want to be involved in decisions about their treatment, and would like to be able to understand the risks of side effects versus the likely benefits of treatment, before they commit to the inconvenience of taking regular medication. An informed patient is more likely to be concordant with treatment, reducing waste of health care

resources including professional time and the waste of medicines which are dispensed but not taken.

Communicating risk is not simple (Paling, 2003). Many different dimensions and inherent uncertainties need to be taken into account, and patients' assessment of risk is primarily determined by emotions, beliefs and values, not facts. This is important, because patients and health care professionals may ascribe different values to the same level of risk. Health care professionals need to be able to discuss risks and benefits with patients in a context that would enable the patient to have the best chance of understanding those risks. It is also prudent to inform the patient that virtually all treatments are associated with some harm and that there is almost always a trade-off between benefit and harm. How health care professionals present risk and benefit can affect the patient's perception of risk.

Some important principles to follow when describing risks and benefit to patients:

- Remember patients' assessments of risk are primarily determined by emotions, not by facts
- Communicate the trade-off between benefits and harms
- Avoid purely descriptive terms of risk, for example 'low risk'
- Use a consistent denominator, for example 1 in 100, 5 in 100; not 1 in 100, 1 in 20
- Use absolute numbers (not relative, or percentages)
- Describe outcomes in both a negative and positive perspective
- Use visual aids and probabilities.

Visual patient decision aids are becoming increasingly popular as a tool that health care professionals can use to support discussions with patients by increasing their knowledge about expected outcomes and helping them to relate these to their personal values (National Prescribing Centre, 2008). Further information about using patient decision aids can be found at http://www.npci.org.uk/therapeutics/mastery/mast4/patient_decision_aids/patient_decision_aid1.php

Adherence

Adherence has been defined as the extent to which a patient's behaviour matches the agreed recommendation from the prescriber. When a patient is non-adherent this can be classified as intentional or unintentional non-adherence (National Institute for Health and Clinical Excellence, 2009).

Unintentional non-adherence occurs when the patient wishes to follow the treatment plan agreed with the prescriber, but is unable to do so because of circumstances beyond their control. Examples of this include forgetting to take the medicine at the defined time or an inability to use the device prescribed. Strategies to overcome such obstacles include medication reminder charts, use of multi-compartment medication dose systems, large print for those with poor eyesight, aids to improve medication delivery, for example inhaler-aids, tube squeezers for ointments and creams, and eye drop administration devices. A selection of these devices is detailed in a guide to the design of dispensed medicines (National Patient Safety Agency, 2007).

Intentional non-adherence occurs when the patient decides he/she does not wish to follow the agreed treatment plan. This may occur because of the patient's beliefs, his/her perceptions or motivation. Therefore, it is important that all of these aspects are included in the discussion between the patient and prescriber when the treatment plan is developed. The patient needs to fully appreciate his/her medical condition and its prognosis in order to understand the rationale for the treatment options discussed. Also the effect of not taking the treatment needs to be explicitly explored with the patient. The benefits of the treatment plan as well as side effects also need to be explored with the patient. The patient information leaflet (PIL) can be used to support this discussion. The patient's previous experience of medicines and associated side effects should be explored as this gives the prescriber vital information about perceptions and motivation. Adherence to existing prescribed medication should be explored non-judgementally. For example, asking the patient how often he/she has missed taking doses at the prescribed time over the previous 7 days would enable the prescriber to assess adherence but also explore lifestyle factors or side effects which may impact on the patient. These can then be discussed and strategies developed to optimise adherence.

Studies have demonstrated that between 35% and 50% of medicines prescribed for chronic conditions are not taken as recommended (National Institute for Health and Clinical Excellence, 2009). Therefore, it is the prescriber's responsibility to explore with the patient their perceptions of medicines to determine if there are any reasons why they may not want to or are unable to use the medicine. In addition, any barriers which might prevent the patient from using the treatment as agreed, for example manual dexterity, eyesight, memory, should be discussed and assessed. Such a frank discussion should enable the patient and prescriber to jointly identify the optimum treatment regimen to treat the condition. In addition, information from the patient's medical records can be used to assess adherence. For example, does the frequency of requests for repeat medication equate to the anticipated duration of use?

Review of unused medicines can be undertaken and it is also important to assess the patient's administration technique on an ongoing basis for devices, for example asthma inhalers to optimise correct technique. This can be achieved, for example, on carrying out a medicine's reconciliation on hospital admission when the patient's prescribed medicines are compared to what they were taking before admission through discussion with patients/carers and review of primary care records.

As it is likely that at some point all patients will forget to take their medicine, it is important to give all patients information on what to do should a dose be missed. For individuals taking medication for treatment of a chronic condition, adherence should not be assumed and therefore assessment of adherence should form an ongoing discussion at each consultation.

Medication review

Medication review has been defined as 'a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste' (Medicines Partnership, 2002).

It is important that medicines are prescribed appropriately and that patients continue to achieve benefits from their medicines. The regular review of medicines is a key part of a good prescribing process and has many potential benefits for patients including:

- Improves the current and future management of the patient's medical condition;
- Provides an opportunity to develop a shared understanding between the patient and the health care professional about medicines and their role in the patient's treatment;
- Improves health outcomes through optimal medicines use;
- Reduces adverse events related to medicines;
- Provides an opportunity to empower the patient and carers to be actively involved in their care and treatment;
- Reduces unwanted or unused medicines.

Many medicines prescribed for patients are used to treat chronic long-term conditions and are consequently prescribed regularly on a long-term basis. Frequently, patients obtain these medicines using a repeat prescribing system. This enables the patients to obtain further supplies of their medicine without routinely having to see their primary care doctor or prescriber, thereby reducing unnecessary consultations. In the UK, repeat prescribing accounts for about 60–75% of all prescriptions and 80% of cost. Robust systems and processes are essential in primary care to ensure repeat prescribing is safe and not wasteful. Reviewing a patient's medication forms an essential element of a robust repeat prescribing process.

Medication reviews can be carried out in many different care settings, by a variety of health care professionals and in many different ways. Different types of medication review are required to meet the needs of patients for different purposes. A medication review can be from a simple review of the prescription to an in-depth clinical medication review. However, the aim of all types of medication review is to achieve the following:

- Give patients the chance to raise questions and highlight problems they are having with their medicines.
- Seek to improve or optimise the benefit of treatment for an individual patient.
- Review should be carried out in a systematic way by a competent health care professional.
- Have any proposed changes from the review agreed with the patient.
- Review should be clearly documented in the patient's medical notes.
- Monitor and record the outcome of any change in medication.

The benefits of medication review are now being recognised by health policy makers, and in the UK, community pharmacists are required to carry out different levels of medication review as part of their normal clinical activities. Medication reviews are often targeted towards patient groups who are more likely to have problems with their medicines, for example the elderly, patients taking more than four medicines regularly, patients in care homes, those on medicines with special monitoring requirements. Characteristics of different types of medication review are described in Table 2.2.

The key elements of an advanced clinical medication review are:

- Pre-planning and advance warning for the patient
- Identifying ALL medicines being taken
- Patient's understanding of treatment

Table 2.2 Characteristics of types of medication review (adapted from Clyne et al., 2008)

	Purpose of the review	Requires patient to be present	Access to patient's notes
Prescription review	Address technical issues relating to the prescription, for example anomalies, changed items, cost-effectiveness	No (any resulting changes to prescribed medicines must involve the patient/carer)	Possibly (community pharmacist may not have access to patient's clinical notes)
Concordance and compliance medication review	Address issues relating to the patient's medicine-taking behaviour and use of medicines	Usually (any resulting changes to prescribed medicines must involve the patient/carer)	Possibly (community pharmacist may not have access to patient's clinical notes)
Clinical medication review	Address issues relating to the patient's use of medicines in the context of their clinical condition	Yes	Yes

Medication reviews include all medicines, including prescription, complementary and over the counter medicines. Prescription review may relate to one therapeutic area only.

- Appropriateness of treatment
- Review of physiological tests and measurements
- Review of efficacy
- Side effects and interactions
- Practicalities of medicines usage
- Future treatment plans
- Opportunities for questions and concerns.

The NO TEARS approach (Lewis, 2004) is also a useful prompt to assist such a review (Table 2.3).

Factors that influence prescribers

A prescriber is subject to various influences which may impact upon their decision making when deciding whether to prescribe a medicine and which medicine to prescribe. Some of these influences may result in poor decision making; therefore, it is important to have an understanding of these influences and how they may impact on prescribing decisions.

A range of influences that affect the prescribing decisions made by primary care doctors have been identified (Fig. 2.3).

Patients and prescribing decisions

The prescribing and use of medicines is strongly influenced by cultural factors that affects patients and prescribers alike. Issues such as whether the patient expects a prescription or whether the prescriber thinks the patient expects a prescription both influence the decision to prescribe. Patients may want a prescription for a whole variety of reasons, some of which are more valid than others. Beyond wanting a medicine for its therapeutic effect, a prescription for a medicine may demonstrate to the patient that their illness is recognised, be seen as a symbol of care, offer legitimacy for time off work because of illness, or fit with their health beliefs. Patients who frequently consult and receive a prescription are more likely to repeat the experience, and expect a prescription at their next consultation.

A number of studies have found that doctors sometimes feel under pressure from patients to prescribe, although patients may not always expect a prescription from the doctor. However, while patients often expect to receive a medicine, they may also have more complex agendas that need to be explored in the consultation. Patients may have mixed attitudes towards medicines and reluctance to take medicines is quite common. Whilst a medicine may be prescribed for its pharmacological effect, there may be other associated reasons

Table 2.3 The NO TEARS approach to medication review

NO TEARS	Questions to think about
*N*eed and indication	Why is the patient taking the medicine, and is the indication clearly documented in the notes? Do they still need the medicine? Is the dose appropriate? Has the diagnosis been confirmed or refuted? Would a non-drug treatment be better? Does the patient know what their medicines are for?
*O*pen questions	Use open questions to find out what the patient understands about their medicines, and what problems they may be having with them.
*T*ests and monitoring	Is the illness under control? Does treatment need to be adjusted to improve control? What special monitoring requirements are there for this patient's medicines? Who is responsible for checking test results?
*E*vidence and guidelines	Is there new evidence or guidelines that mean I need to review the patient's medicines? Is the dose still appropriate? Do I need to do any other investigations or tests?
*A*dverse effects	Does the patient have any side effects? Are any of the patient's symptoms likely to be caused by side effects of medicines, including OTC and complementary medicines? Are any of the patients' medicines being used to treat side effects of other medicines? Is there any new advice or warnings on side effects or interactions?
*R*isk reduction and prevention	If there is time, ask about alcohol use, smoking, obesity, falls risk or family history, for opportunistic screening. Is treatment optimised to reduce risks?
*S*implification and switches	Can the patient's medicines regimen be simplified? Are repeat medicines synchronised for prescribing at the same time? Explain any changes in medicines to the patient.

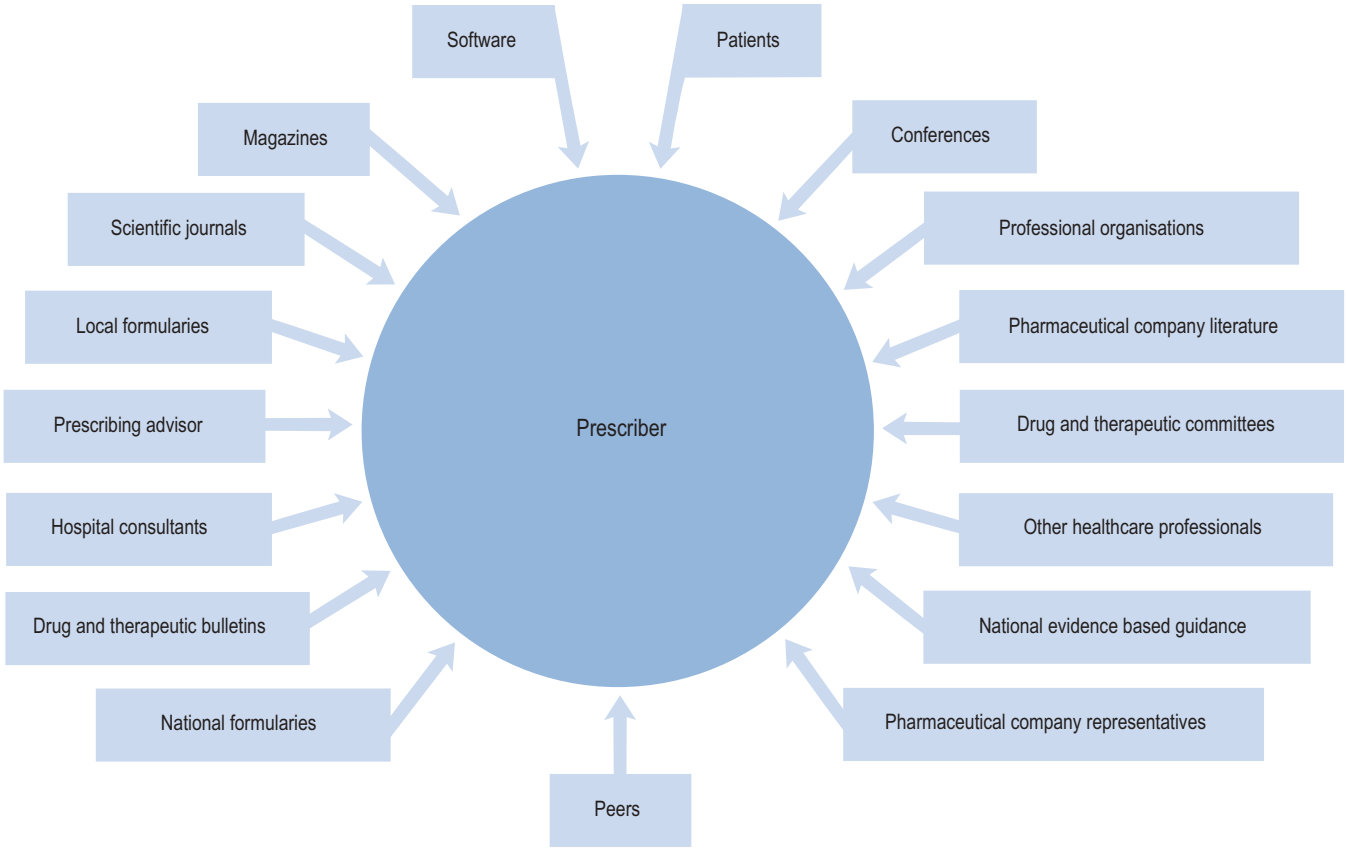

Fig. 2.3 Influences on prescribing decisions.

to prescribe for a patient, for example to end the consultation, to avoid doing anything else or having to say 'no', to maintain contact with the patient, as a response to carer anxiety, or to fulfil the patient's expectation.

The informed patient

Health care is moving to a position of greater shared decision making with patients and development of the concept of patient autonomy. This is being supported through the better provision of information for patients about their prescribed medicines. The EU directive 2001/83 (European Commission, 2001) requires that all pharmaceutical products are packaged with an approved PIL, which provides information on how to take the medicine and possible adverse effects. Other important developments that have increased patients' access to information, albeit of variable quality, include the role of the media in general and the amount of attention they give to health and health-related matters, the emergence of the Internet, and the development of patient support groups. The reporting in the media of concerns regarding the safety of MMR vaccine and the subsequent rapid drop in MMR vaccinations rates in children is a good example of the importance of these developments in influencing patients and prescribing.

Direct advertising of medicines to patients is allowed in the USA and New Zealand, but not in Europe. Advertising medicines in this way is clearly effective in increasing sales of medicines, as evidenced by the increased spending and prescriptions for advertised drugs, compared to non-advertised drugs in these countries. This has led to concern that direct to consumer advertising encourages unnecessary and inappropriate use of medication. In the UK, education for patients may be provided by the manufacturer through sponsored disease awareness campaigns but there is concern that these encourage individuals to seek advice or treatment from their doctor for conditions that have been incorrectly self diagnosed. These campaigns may also help to raise awareness of conditions that have not been well managed in the past. However, they can also act as covert advertisements for prescription. Such campaigns, which may be established by a drug company with or without the endorsement of a patient group, often take place at the same time as a drug's launch and may involve aggressive promotion. As a consequence there have been calls to control the influence of companies on the production of disease awareness campaigns that impact on the individual patient, who then exerts pressure on the prescriber for a specific medicine.

Health care policy

National policy and guidelines, for example National Service Frameworks and guidance from NICE in the UK, have a significant influence on prescribing, although the influence may not be as great as expected for some medicines (Prescribing Support Unit, 2009).

Colleagues

Several studies have found that health care professionals in primary care (both doctors and nurses) rely on advice from trusted colleagues and opinion leaders as a key source of information on how to manage patients. It has been estimated that 40% of prescribing in primary care was strongly influenced by hospitals because the choice of medicine prescribed in general practice was often guided by hospital specialists through their precedent prescribing and educational advice (National Audit Office, 2007). The Pharmaceutical Industry recognise the value of identifying 'key opinion' leaders amongst the medical community and will try to cultivate them to influence their peers and fellow clinicians, by paying them for a consultancy, lecture fees, travel, research and articles favourable to that company's products.

Pharmacists, in both the primary and secondary care, themselves have an influence on prescribing through their roles as clinical pharmacists, or as part of their work advising on prescribing in primary care. Pharmacists are often regarded as trusted colleagues, and as such can have an important influence on prescribing. In whichever sector they are working, pharmacists need to be aware that their advice and decisions may be influenced by exactly the same factors that influence the prescriber.

Pharmaceutical industry

The pharmaceutical industry has a very wide and important influence on prescribing decisions affecting every level of health care provision, from the medicines that are initially discovered and developed through clinical trials, to the promotion of medicines to the prescriber and patient groups, the prescription of medicines and the compilation of clinical guidelines. There are over 8000 pharmaceutical company representatives in the UK trying to persuade prescribers to prescribe their company's product. This represents a ratio of about 1 representative for every 7.5 doctors (House of Commons Health Committee, 2005) with 1 representative for every 4 primary care doctors (National Audit Office, 2007). Whilst representatives from the pharmaceutical industry can provide useful and important new information to prescribers about medicines, the information presented is not without bias and rarely provides any objective discussion of available competitor products.

The influence of the pharmaceutical industry extends well beyond the traditional selling approach of using representatives, and is increasingly sophisticated. The pharmaceutical industry spends millions on advertising, company sponsored information from medical journals and supplements, sponsorship to attend conferences and meetings, and medical education. Over half of postgraduate education and training for doctors in the UK is sponsored by the pharmaceutical industry. The wide variety, volume and intensity of marketing activities the industry engage in are an important influence on prescribing by health care professionals. But on asking prescribers if they are influenced by the pharmaceutical industry, they usually deny that drug promotion affects their own prescribing practices, although they do believe that it affects other prescribers' prescribing habits. This is clearly not the case, as research has shown that even the use of modest samples, gifts and food exerts a significant influence on prescriber behaviour.

Cognitive factors

Most prescribing decisions are made using the processes our brains develop to handle large volumes of complex information quickly. This rapid decision making is aided by heuristics, strategies that provide shortcuts that allow us to make quick decisions. This type of decision making largely relies on a small number of variables that we believe are important based on information collected by brief reading in summary journals (e.g. Bandolier, Drug and Therapeutics Bulletin and articles in popular doctors' and nurses' magazines mailed free of charge) and talking to colleagues. However, it is important to recognise that cognitive biases affect these heuristics (or shortcuts) involved in rapid decision making, and that experts as well as generalists are just as fallible to cognitive biases in decision making. At least 43 cognitive biases in decision making have been described. Some examples of cognitive biases that may affect prescribing decisions are shown in Table 2.4.

Table 2.4 Examples of types of cognitive biases that influence prescribing

Type of cognitive bias	Description
Novelty preference	The belief that the progress of science always results in improvements and that newer treatments are generally better than older treatments
Over optimism bias	Tendency of people to over-estimate the outcome of actions, events or personal attributes to a positive skew
Confirmation bias	Information that confirms one's already firmly held belief is given higher weight than refuting evidence
Mere exposure effect	More familiar ideas or objects are preferred or given greater weight in decision making
Loss aversion	To weigh the avoidance of loss more greatly than the pursuit of an equivalent gain
Illusory correlation	The tendency to perceive two events as causally related, when in fact the connection between them is coincidental or even non-existent

Strategies to influence prescribing

Health care organisations at local and national levels have been seeking to influence prescribing behaviour over many years, both to control expenditure on medicines and to improve quality of care. Medicines are one of the most well-researched interventions in health care, with a relative wealth of evidence to support their use. Despite this, there is still a wide variation in prescribing practice between clinicians and between health care organisations. This may reflect variation in clinical practice arising from the inconsistent implementation of evidence-based medicine and the impact of the many factors that influence prescribing. Strategies to improve prescribing can be managerial and process orientated, or more supportive and educationally orientated. Strategies that use a combination of different interventions on a repeat basis are more likely to be successful at influencing prescribing.

Managerial approaches to influence prescribing

Formularies are restricted lists of medicines, to which prescribers are encouraged or required to adhere. This helps consistency of prescribing, ensures that prescribers are familiar with a range of medicines, and can help contain costs. In secondary care, prescribers can usually only prescribe those medicines included within the formulary, as these are the medicines stocked in the pharmacy. In primary care a formulary is generally advisory in nature and less restrictive as community pharmacies can supply any reimbursable medicine. Medicines are included in a formulary if they are deemed to have met rational criteria based on clinical and cost-effectiveness. Health care organisations usually have a process for deciding which medicines are included within their local formulary, keeping the formulary updated, and monitoring the implementation of local formulary decisions. Some formularies are developed to cover prescribing in both primary and secondary care, which mean they can have a significant influence on prescribing patterns in the whole of a local health economy. Over recent years, formularies have developed beyond just being a list of medicines and often include useful advice for prescribers, for example about disease management.

Local and national guidelines

Guidelines for the use of a medicine, a group of medicines or the management of a clinical condition may be produced for local or national use. They can be useful tools to guide and support prescribers in choosing which medicines they should prescribe. Ideally, guidelines should make evidence-based standards of care explicit and accessible, and aid clinical decision making. The best-quality guidelines are usually those produced using systematically developed evidence-based statements to assist clinicians in making decisions about appropriate health care for specific clinical circumstances. In the UK, there is an accreditation scheme to recognise organisations who achieve high standards in producing health or social care guidance. Examples of accredited guidelines are those produced by NICE (National Institute for Health and Clinical Excellence, www.nice.org.uk) and SIGN (Scottish Intercollegiate Guideline Network, www.sign.ac.uk). Local guidelines are often developed to provide a local context and interpretation of national guidance, and offer guidance on managing patients between primary and secondary care. However, despite the availability of good quality accessible clinical guidelines, implementation in practice remains variable.

Clinical decision support systems are increasingly popular as a way of improving clinical practice, and influence prescribing. These often utilise interactive computer programs that help clinicians with decision-making tasks at the point of care, and also help them keep up-to-date, and support implementation of clinical guidelines. Clinical knowledge summaries (www.cks.nhs.uk) is a decision support system developed for use in primary care that includes PILs, helps with differential diagnosis, suggests investigations and referral criteria, and gives screens that can be shared between the patient and the prescriber in the surgery.

Incentives

In an effort to contain prescribing costs, some health care systems use direct incentives to influence clinical behaviour and, in particular, prescribing. The incentives, which are usually financial, may be direct to the prescriber or offer some benefits to the prescriber's patients. They can have a significant impact on prescribing practice. Typically, primary care doctors are given indicative prescribing budgets and are expected to meet the prescribing needs of their patients from within this budget. Financial incentive schemes to reward good fiscal management of prescribing budgets and improve the quality of prescribing are used to encourage prescribers to change their practice. Incentive schemes usually influence what is prescribed, rather than whether a prescription is written. The most effective schemes are simple to understand, have achievable targets, and require information about prescribing patterns to be readily available. However, incentives schemes for prescribing need to be managed carefully in order not to create perverse incentives, such as increasing the referral of patients to another part of the health care system, or causing an increase in overall health care costs.

Provision of comparative (benchmarking) information

The provision of benchmarked information on comparative prescribing patterns to primary care doctors is an important influence on prescribing behaviour. Using appropriate benchmarking data brings the behaviour of practices into a local and national context. Benchmarking can provide the basis for making clinicians aware of the potential for change and allows them to understand the potential outcome of any actions. Various prescribing indicators have been developed both locally and nationally to measure and compare quality and cost-effectiveness of prescribing. Ideally, indicators used should be evidence based, utilise available data sources and be validated.

Support and education

One of the challenges for modern health care organisations is to ensure consistent implementation of evidence-based interventions and influence clinical practice. Simply providing prescribers with information or education about an evidence-based intervention rarely produces a change in practice. There is a need to understand the concerns that the adopting clinician may have about the change, recognise that these concerns are often legitimate but may change over time and that the concerns must be addressed and overcome before successful adoption can occur. Interpersonal influence, particularly through the use of trusted colleagues or opinion leaders, is a powerful way to change practice. This is the basis for using pharmacists as prescribing advisers or 'academic detailers' to influence prescribing practice particularly in primary care. Prescribing advisers present evidence-based tailored messages, allow the exchange of information and try to negotiate and persuade clinicians to change practice. Clinicians see pharmacists as a trusted and credible source of prescribing information, who can be moderately successful in changing practice, particularly if linked with an incentive.

In order to change prescribing practice, pharmacists need to be aware of how to use an adoption model-based approach to convey key messages to the prescriber to help them change practice. One such model is known as AIDA (see Table 2.5)

More sophisticated multifaceted educational interventions can also be effective at changing prescribing behaviour but need to be flexible to meet the needs of individual clinicians. This sort of combination approach includes small group learning, audit and feedback, practical support to make changes in practice, and involvement and education of patients.

Table 2.5 AIDA adoption model for influencing prescribers

Awareness	Make the prescriber aware of the issues, prescribing data and evidence for the need to change
Interest	Let the prescriber ask questions and find out more about the proposed change: what the benefits are, what the prescriber's concerns are
Decision	Help the prescriber come to a decision to make a change. How can the change be applied to their patients, what support is there to overcome the barriers to change, provide further information and training to support the change
Action	Action of making a change by the prescriber. Support this with simple reminders, patient decision support, feedback data and audit

Conclusion

While medicines have the capacity to improve health, they also have the potential to cause harm. Prescribing of medicines needs to be rational and effective in order to maximise benefit and minimise harm. Good prescribing should ensure the patient's ideas, concerns and expectations are taken into account. This can be effectively managed by adopting a consultation framework and using patient decision aids to support shared decision making with the patient. Prescribers need to be aware of their responsibilities and accountability particularly when prescribing off-label or unlicensed medicines. They also need to work within their organisation's clinical governance framework. The influences and biases that affect prescribing need to be recognised and minimised by utilising trusted independent sources of information to inform prescribing decisions.

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3 Practical pharmacokinetics

R. Fitzpatrick and A. Kostrzewski

Key points

- Pharmacokinetics can be applied to a range of clinical situations with or without therapeutic drug monitoring (TDM).
- TDM can improve patient outcomes but is only necessary for drugs with a low therapeutic index, where there is a good concentration response relationship, and where there is no easily measurable physiological parameter.
- Sampling before steady state is reached or before distribution is complete, leads to erroneous results.
- The volume of distribution can be used to determine the loading dose.
- The elimination half-life determines the time to steady state and the dosing interval.
- Kinetic constants determine the rate of absorption and elimination.
- Clearance determines the maintenance dose.
- Creatinine clearance can be reliably estimated from population values.
- Use of actual blood level data wherever possible to assist dose adjustment is advisable. However, population pharmacokinetic values can be used for digoxin, theophylline and gentamicin.
- Once daily dosing of gentamicin is a realistic alternative to multiple dosing.
- TDM is essential in the dose titration of lithium and phenytoin, but of little value for valproate, or the newer anticonvulsants.

Clinical pharmacokinetics may be defined as the study of the time course of the absorption, distribution, metabolism and excretion of drugs and their corresponding pharmacological response. In practice, pharmacokinetics makes it possible to model what may happen to a drug after it has been administered to a patient. Clearly, this science may be applied to a wide range of clinical situations, hence the term 'clinical pharmacokinetics'. However, no matter how elegant or precise the mathematical modelling, the relationship between concentration and effect must be established before pharmacokinetics will be of benefit to the patient.

General applications

Clinical pharmacokinetics can be applied in daily practice to drugs with a low therapeutic index, even if drug level monitoring is not required.

Time to maximal response

By knowing the half-life of a drug, the time to reach a steady state may be estimated (Fig. 3.1), and also when the maximal therapeutic response is likely to occur, irrespective of whether drug level monitoring is needed.

Need for a loading dose

The same type of information can be used to determine whether the loading dose of a drug is necessary, since drugs with longer half-lives are more likely to require loading doses for acute treatment.

Dosage alterations

Clinical pharmacokinetics can be useful in determining dosage alteration if the route of elimination is impaired through end organ failure (e.g. renal failure) or drug interaction. Using limited pharmacokinetic information such as the fraction that should be excreted unchanged (f_e value), which can be found in most pharmacology textbooks, quantitative dosage changes can be estimated.

Choosing a formulation

An understanding of the pharmacokinetics of absorption may also be useful in evaluating the appropriateness of particular formulations of a drug in a patient.

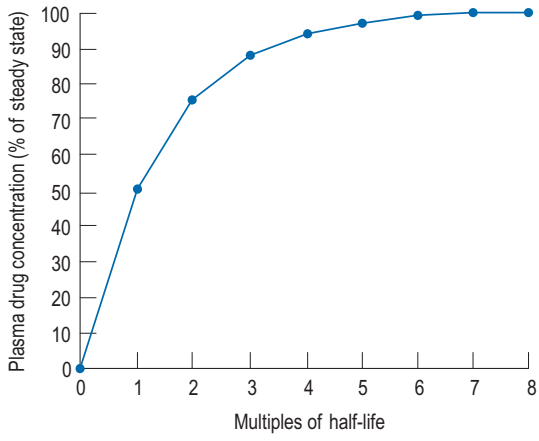


Fig. 3.1 Time to steady state.

Application to therapeutic drug monitoring

Clinical pharmacokinetics is usually associated with therapeutic drug monitoring (TDM), and its subsequent utilisation. When TDM is used appropriately, it has been demonstrated that patients suffer fewer side effects than those who are not monitored (Reid et al., 1990). Although TDM is a proxy outcome measure, a study with aminoglycosides (Crist et al., 1987) demonstrated shorter hospital stays for patients where TDM was used. Furthermore, a study on the use of anticonvulsants (McFadyen et al., 1990) showed better epilepsy control in those patients where TDM was used. A literature review of the cost-effectiveness of TDM concluded that emphasis on just cost is inappropriate and clinical relevance should be sought (Touw et al., 2007). There are various levels of sophistication for the application of pharmacokinetics to TDM. Knowledge of the distribution time and an understanding of the concept of steady state can facilitate determination of appropriate sampling times.

For most drugs that undergo first-order elimination, a linear relationship exists between dose and concentration, which can be used for dose adjustment purposes. However, if the clearance of the drug changes as the concentration changes (e.g. phenytoin), then an understanding of the drug's pharmacokinetics will assist in making correct dose adjustments.

More sophisticated application of pharmacokinetics involves the use of population pharmacokinetic data to produce initial dosage guidelines, for example nomograms for digoxin and gentamicin, and to predict drug levels. Pharmacokinetics can also assist in complex dosage individualisation using actual patient specific drug level data.

Given the wide range of clinical situations in which pharmacokinetics can be applied, pharmacists must have a good understanding of the subject and of how to apply it to maximise their contribution to patient care.

Basic concepts

Volume of distribution

The apparent volume of distribution (V_d) may be defined as the size of a compartment which will account for the total amount of drug in the body (A) if it were present in the same concentration as in plasma. This means that it is the apparent volume of fluid in the body which results in the measured concentration of drug in plasma (C) for a known amount of drug given, that is:

$$C = \frac{A}{V_d}$$

This relationship assumes that the drug is evenly distributed throughout the body in the same concentration as in the plasma. However, this is not the case in practice, since many drugs are present in different concentrations in various parts of the body. Thus, some drugs which concentrate in muscle tissue have a very large apparent volume of distribution, for example digoxin. This concept is better explained in Fig. 3.2.

The apparent volume of distribution may be used to determine the plasma concentration after an intravenous loading dose:

$$C = \frac{\text{loading dose}}{V_d} \quad (1)$$

Conversely, if the desired concentration is known, the loading dose may be determined:

$$\text{loading dose} = \text{desired } C \times V_d \quad (2)$$

In the previous discussion, it has been assumed that after a given dose a drug is instantaneously distributed between the various tissues and plasma. In practice this is seldom the case. For practical purposes it is reasonable to generalise by referring to plasma as one compartment and tissue as if it were another single separate compartment. However, in reality there will be many tissue subcompartments. Thus, in pharmacokinetic terms the body may be described as if it were divided into two compartments: the plasma and the tissues.

Figure 3.3 depicts the disposition of a drug immediately after administration and relates this to the plasma concentration–time graph.

Initially, the plasma concentration falls rapidly, due to distribution and elimination (α phase). However, when an equilibrium is reached between the plasma and tissue (i.e. the distribution is complete), the change in plasma concentration is only due to elimination from the plasma (β phase), and the plasma concentration falls at a slower rate. The drug is said to follow a two-compartment model. However, if distribution

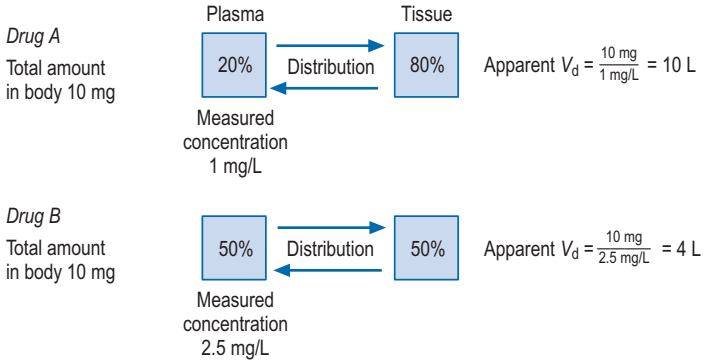


Fig. 3.2 Distribution: more of drug A is distributed in the tissue compartment resulting in a higher apparent volume of distribution than drug B, where more remains in the plasma.

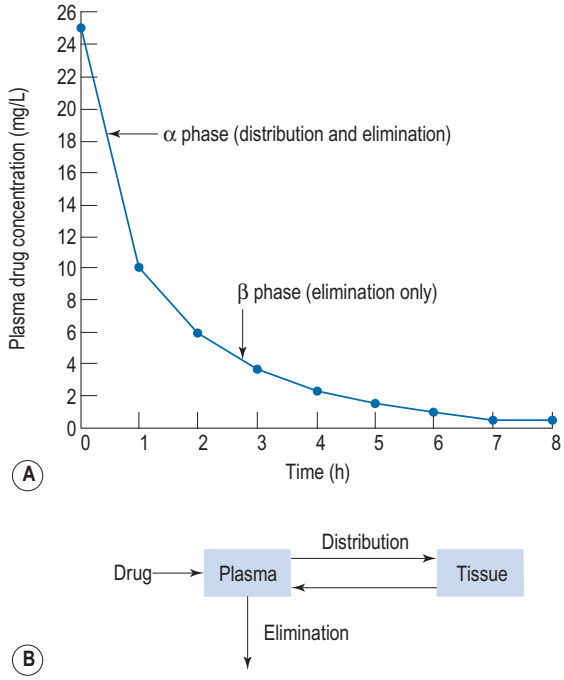


Fig. 3.3 (A) Two-compartment model showing two phases in the plasma concentration–time profile. (B) Representation of a two-compartment model showing distribution of drug between plasma and tissue compartments.

is completed quickly (within minutes), then the α phase is not seen, and the drug is said to follow a one-compartment model.

The practical implications of a two-compartment model are that any sampling for monitoring purposes should be carried out after distribution is complete. In addition, intravenous bolus doses are given slowly to avoid transient side effects caused by high peak concentrations.

Elimination

Drugs may be eliminated from the body by a number of routes. The primary routes are excretion of the unchanged drug in the kidneys, or metabolism (usually in the liver) into a more water soluble compound for subsequent excretion in the kidneys, or a combination of both.

The main pharmacokinetic parameter describing elimination is clearance (CL). This is defined as the volume of plasma completely emptied of drug per unit time. For example, if the concentration of a drug in a patient is 1 g/L and the clearance is 1 L/h, then the rate of elimination will be 1 g/h. Thus, a relationship exists:

$$\text{rate of elimination} = \text{CL} \times C \qquad (3)$$

Total body elimination is the sum of the metabolic rate of elimination and the renal rate of elimination. Therefore:

$$\text{total body clearance} = \text{CL (metabolic)} + \text{CL (renal)}$$

Thus, if the fraction eliminated by the renal route is known (f_e), then the effect of renal impairment on total body clearance can be estimated.

The clearance of most drugs remains constant for each individual. However, it may alter in cases of drug interactions, changing end-organ function or autoinduction. Therefore, it is clear from equation (Eq.) (3) that as the plasma concentration changes so will the rate of elimination. However, when the rate of administration is equal to the rate of elimination, the plasma concentration is constant (C^{ss}) and the drug is said to be at a steady state.

At steady state:

$$\text{rate in} = \text{rate out}$$

At the beginning of a dosage regimen the plasma concentration is low. Therefore, the rate of elimination from Eq. (3) is less than the rate of administration, and accumulation occurs until a steady state is reached (see Fig. 3.1).

$$\text{rate of administration} = \text{rate of elimination} = \text{CL} \times C^{ss} \qquad (4)$$

It is clear from Eq. (3) that as the plasma concentration falls (e.g. on stopping treatment or after a single dose), the rate of elimination also falls. Therefore, the plasma concentration–time graph follows a non-linear curve characteristic of this type of first-order elimination (Fig. 3.4). This is profoundly different from a constant rate of elimination irrespective of plasma concentration, which is typical of zero-order elimination.

For drugs undergoing first-order elimination, there are two other useful pharmacokinetic parameters in addition to the volume of distribution and clearance. These are the elimination rate constant and elimination half-life.

The elimination rate constant (k_e) is the fraction of the amount of drug in the body (A) eliminated per unit time. For example, if the body contains 100 mg of a drug and 10% is eliminated per unit time, then $k_e = 0.1$. In the first unit of time, 0.1×100 mg or 10 mg is eliminated, leaving 90 mg. In the second unit of time, 0.1×90 mg or 9 mg is eliminated, leaving 81 mg. Elimination continues in this manner. Therefore:

$$\text{rate of elimination} = k_e \times A \qquad (5)$$

Combining Eqs. (3) and (5) gives

$$\text{CL} \times C = k_e \times A$$

and since

$$C = \frac{A}{V_d}$$

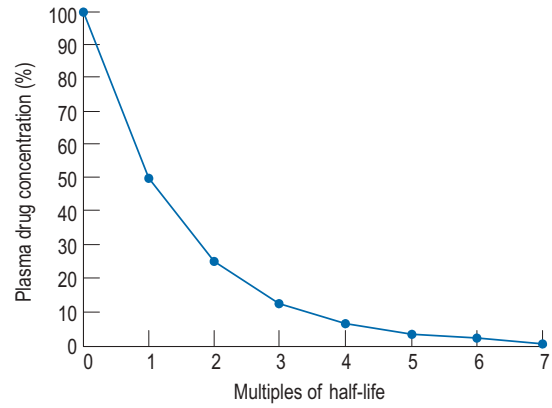


Fig. 3.4 First-order elimination.

then

$$\mathrm{CL} \times \frac{A}{V_d} = k_e \times A$$

Therefore,

$$\mathrm{CL} = k_e \times V_d \quad (6)$$

Elimination half-life ($t_{1/2}$) is the time it takes for the plasma concentration to decay by half. In five half-lives the plasma concentration will fall to approximately zero (see Fig. 3.4).

The equation which is described in Fig. 3.4 is

$$C_2 = C_1 \times e^{-k_e \times t} \quad (7)$$

where C_1 and C_2 are plasma concentrations and t is time.

If half-life is substituted for time in Eq. (7), C_2 must be half of C_1.

Therefore,

$$0.5 \times C_1 = C_1 \times e^{-k_e \times t_{1/2}}$$

$$0.5 = e^{-k_e \times t_{1/2}}$$

$$\ln 0.5 = -k_e \times t_{1/2}$$

$$0.693 = -k_e \times t_{1/2}$$

$$t_{1/2} = \frac{0.693}{k_e} \quad (8)$$

There are two ways of determining k_e, either by estimating the half-life and applying Eq. (8) or by substituting two plasma concentrations in Eq. (7) and applying natural logarithms:

$$\ln C_2 = \ln C_1 - (k_e \times t)$$

$$k_e \times t = \ln C_1 - \ln C_2$$

$$k_e = \frac{\ln C_1 - \ln C_2}{t}$$

In the same way as it takes approximately five half-lives for the plasma concentration to decay to zero after a single dose, it takes approximately five half-lives for a drug to accumulate to the steady state on repeated dosing or during constant infusion (see Fig. 3.1).

This graph may be described by the equation

$$C = C^{ss}[1 - e^{-k_e \times t}] \quad (9)$$

where C is the plasma concentration at time t after the start of the infusion and C^{ss} is the steady state plasma concentration. Thus (if the appropriate pharmacokinetic parameters are known), it is possible to estimate the plasma concentration any time after a single dose or the start of a dosage regimen.

Absorption

In the preceding sections, the intravenous route has been discussed, and with this route all of the administered drug is absorbed. However, if a drug is administered by any other route it must be absorbed into the bloodstream. This process may or may not be 100% efficient.

The fraction of the administered dose which is absorbed into the bloodstream is the bioavailability (F). Therefore, when applying pharmacokinetics for oral administration, the dose or rate of administration must be multiplied by F. Bioavailability F is determined by calculating the area under the concentration time curve (AUC). The rationale for this is described below.

The rate of elimination of a drug after a single dose is given by Eq. (3). By definition the rate of elimination is amount of drug eliminated per unit time.

The amount eliminated in any one unit of time $\mathrm{d}t = \mathrm{CL} \times C \times \mathrm{d}t$

$$\text{The total amount of drug eliminated} = \sum_0^\infty \mathrm{CL} \times C \times \mathrm{d}t$$

As previously explained, CL is constant. Therefore,

$$\text{Total amount eliminated} = \mathrm{CL} \times \sum C \times \mathrm{d}t \text{ from start until } C \text{ is zero.}$$

$\sum C \times \mathrm{d}t$ from start until zero is actually the area under the plasma concentration–time curve (Fig. 3.5).

After a single i.v. dose the total amount eliminated is equal to the amount administered D i.v.

Therefore, $\mathrm{D\ i.v.} = \mathrm{CL} \times \mathrm{AUC\ i.v.}$ or $\mathrm{CL} = \mathrm{D\ i.v.}/\mathrm{AUC}$.

However, for an oral dose the amount administered is $F \times \mathrm{D\ p.o.}$

As CL is constant in the same individual,

$$\mathrm{CL} = F \times \mathrm{D\ p.o.}/\mathrm{AUC\ p.o.} = \mathrm{D\ i.v.}/\mathrm{AUC\ i.v.}$$

Rearranging gives

$$F = (\mathrm{D\ i.v.} \times \mathrm{AUC\ p.o.})/(\mathrm{D\ p.o.} \times \mathrm{AUC\ i.v.})$$

In this way, F can be calculated from plasma concentration–time curves.

Dosing regimens

From the preceding sections, it is possible to derive equations which can be applied in clinical practice.

From Eq. (1) we can determine the change in plasma concentration ΔC immediately after a single dose:

$$\Delta C = \frac{S \times F \times \mathrm{dose}}{V_d} \quad (10)$$

where F is bioavailability and S is the salt factor, which is the fraction of active drug when the dose is administered as a salt (e.g. aminophylline is 80% theophylline, therefore $S = 0.8$).

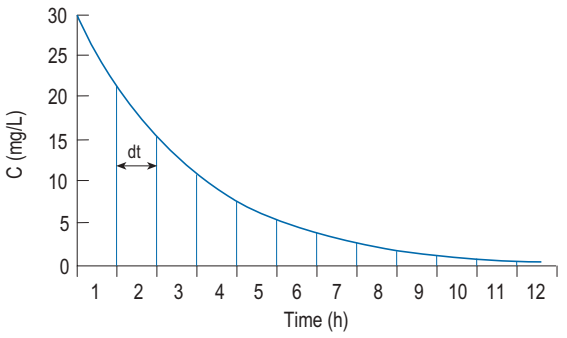


Fig. 3.5 The area under the concentration time curve (AUC) is the sum of C × *dt*.

Conversely, to determine a loading dose:

$$\text{loading dose} = \frac{\text{desired change in } C \times V_d}{S \times F} \quad (11)$$

At the steady state it is possible to determine maintenance dose or steady state plasma concentrations from a modified Eq. (4):

$$\text{rate in} = \frac{S \times F \times \text{dose}}{T} = \text{CL} \times \text{average } C^{ss} \quad (12)$$

where T is the dosing interval.

Peak and trough levels

For oral dosing and constant intravenous infusions, it is usually adequate to use the term 'average steady state plasma concentration' (average C^{ss}). However, for some intravenous bolus injections it is sometimes necessary to determine peak and trough levels (e.g. gentamicin).

At the steady state, the change in concentration due to the administration of an intravenous dose will be equal to the change in concentration due to elimination over one dose interval:

$$\Delta C = \frac{S \times F \times \text{dose}}{V_d} = C_{max} - C_{min}$$

Within one dosing interval the maximum plasma concentration (C^{ss}_{max}) will decay to the minimum plasma concentration (C^{ss}_{min}) as in any first-order process.

Substituting C^{ss}_{max} for C_1 and C^{ss}_{min} for C_2 in Eq. (7):

$$C^{ss}_{max} = C^{ss}_{max} \times e^{-k_e \times t}$$

where t is the dosing interval.

If this is substituted into the preceding equation:

$$\frac{S \times F \times \text{dose}}{V_d} = C^{ss}_{max} - (C^{ss}_{max} \times e^{-k_e \times t})$$

Therefore,

$$C^{ss}_{max} = \frac{S \times F \times \text{dose}}{V_d[1 - e^{-k_e \times t}]} \quad (13)$$

$$C^{ss}_{min} = \frac{S \times F \times \text{dose}}{V_d(1 - e^{-k_e \times t})} \times e^{-k_e \times t} \quad (14)$$

Interpretation of drug concentration data

The availability of the technology to measure the concentration of a drug in plasma should not be the reason for monitoring. There are a number of criteria that should be fulfilled before therapeutic drug monitoring is undertaken. These are:

- the drug should have a low therapeutic index;
- there should be a good concentration–response relationship;
- there are no easily measurable physiological parameters.

In the absence of these criteria being fulfilled, the only other justification for undertaking TDM is to monitor adherence or to confirm toxicity. When interpreting TDM data, a number of factors need to be considered.

Sampling times

In the preceding sections, the time to reach the steady state has been discussed. When TDM is carried out as an aid to dose adjustment, the concentration should be at steady state. Therefore, approximately five half-lives should elapse after initiation or after changing a maintenance regimen, before sampling. The only exception to this rule is when toxicity is suspected. When the steady state has been reached, it is important to sample at the correct time. It is clear from the discussion above that this should be done when distribution is complete (see Fig. 3.3).

Dosage adjustment

Under most circumstances, provided the preceding criteria are observed, adjusting the dose of a drug is relatively simple, since a linear relationship exists between the dose and concentration if a drug follows first-order elimination (Fig. 3.6A). This is the case for most drugs.

Capacity limited clearance

If a drug is eliminated by the liver, it is possible for the metabolic pathway to become saturated, since it is an enzymatic system. Initially the elimination is first-order, but once saturation of the system occurs, elimination becomes zero-order. This results in the characteristic dose–concentration graph seen in Fig. 3.6B. For the majority of drugs eliminated by the liver, this effect is not seen at normal therapeutic doses and only occurs at very high supratherapeutic levels, which is why the kinetics of some drugs in overdose is different from normal. However, one important exception is phenytoin, where saturation of the enzymatic pathway occurs at therapeutic doses. This will be dealt with in the section on phenytoin.

Increasing clearance

The only other situation where first-order elimination is not seen is where clearance increases as the plasma concentration increases (Fig. 3.6C). Under normal circumstances, the plasma protein binding sites available to a drug far outnumber

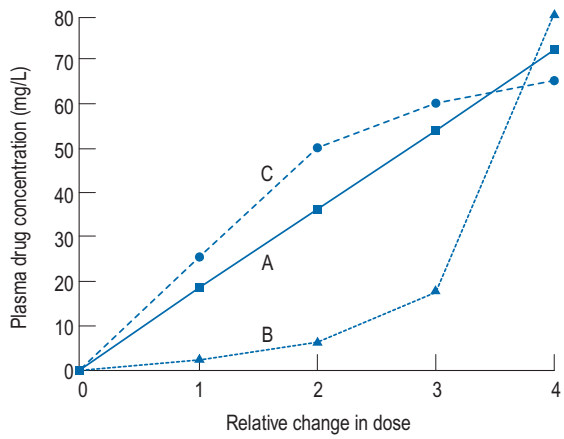


Fig. 3.6 Dose–concentration relationships: (A) first-order elimination, (B) capacity-limited clearance, (C) increasing clearance.

the capacity of the drug to fill those binding sites, and the proportion of the total concentration of drug which is protein bound is constant. However, this situation is not seen in one or two instances (e.g. valproate and disopyramide). For these particular drugs, as the concentration increases the plasma protein binding sites become saturated and the ratio of unbound drug to bound drug increases. The elimination of these drugs increases disproportionate to the total concentration, since elimination is dependent on the unbound concentration.

Therapeutic range

Wherever TDM is carried out, a therapeutic range is usually used as a guide to the optimum concentration. The limits of these ranges should not be taken as absolute. Some patients may respond to levels above or below these ranges, whereas others may experience toxic effects within the so-called therapeutic range. These ranges are only adjuncts to dose determination, which should always be done in the light of clinical response.

Clinical applications

Estimation of creatinine clearance

Since many drugs are renally excreted, and the most practical marker of renal function is creatinine clearance, it is often necessary to estimate this in order to undertake dosage adjustment in renal impairment. The usual method is to undertake a 24-h urine collection coupled with a plasma creatinine measurement. The laboratory then estimates the patient's creatinine clearance. The formula used to determine creatinine clearance is based upon the pharmacokinetic principles in Eq. (3).

The rate of elimination is calculated from the measurement of the total amount of creatinine contained in the 24-h urine sample divided by 24, that is,

$$\frac{\text{amount of creatinine}}{24} = \text{rate of excretion (mg/h)}$$

Using this rate of excretion and substituting the measured plasma creatinine for C^{ss} in Eq. (4), the creatinine clearance can be calculated.

However, there are practical difficulties with this method. The whole process is cumbersome and there is an inevitable delay in obtaining a result. The biggest problem is the inaccuracy of the 24-h urine collection.

An alternative approach is to estimate the rate of production of creatinine (i.e. rate in) instead of the rate of elimination (rate out). Clearly this has advantages, since it does not involve 24-h urine collections and requires only a single measure of plasma creatinine. There are data in the literature relating creatinine production to age, weight and sex since the primary source of creatinine is the breakdown of muscle.

Therefore, equations have been produced which are rearrangements of Eq. (4), that is,

$$\text{creatinine clearance} = \frac{\text{rate of production}}{C^{ss}}$$

Rate of production is replaced by a formula which estimates this from physiological parameters of age, weight and sex.

It has been shown that the equation produced by Cockcroft and Gault (1976) appears to be the most satisfactory. A modified version using SI units is shown as

$$\frac{\text{creatinine clearance}}{(\text{mL/min})} = \frac{F \times [(140 - \text{age in years}) \times \text{weight (kg)}]}{\text{plasma creatinine } (\mu\text{mol/L})}$$

where $F = 1.04$ (females) or 1.23 (males).

There are limitations using only plasma creatinine to estimate renal function. The modification of diet in renal disease (MDRD) formula can be used to estimate glomerular filtration rate (eGFR). This formula uses plasma creatinine, age, sex and ethnicity (Department of Health, 2006).

$$\text{eGFR} = 175 \times [\text{plasma creatinine } (\mu\text{mol/L}) \times 0.011312]^{-1.154} \times [\text{age in year}]^{-0.203} \times [1.212 \text{ if patient is black}] \times [0.742 \text{ if female}]$$

eGFR = glomerular filtration rate (mL/min per 1.73 m^2).

The MDRD should be used with care when calculating doses of drugs, as most of the published dosing information is based on Cockcroft and Gault formula. In patients with moderate to severe renal failure, it is best to use the Cockcroft and Gault formula to determine drug dosing.

Digoxin

Action and uses

Digoxin is the most widely used of the digitalis glycosides. Its primary actions on the heart are those of increasing the force of contraction and decreasing conduction through the atrioventricular node. Currently, its main role is in the treatment of atrial fibrillation by slowing down the ventricular response, although it is also used in the treatment of heart failure in the presence of sinus rhythm. The primary method of monitoring its clinical effect in atrial fibrillation is by measurement of heart rate but knowledge of its pharmacokinetics can be helpful in predicting a patient's dosage requirements.

Plasma concentration–response relationship

- <0.5 µcg/L: no clinical effect
- 0.7 µcg/L: some positive inotropic and conduction blocking effects
- 0.8–2 µcg/L: optimum therapeutic range (0.5–0.9 µcg/L in patients >65)
- 2–2.5 µcg/L: increased risk of toxicity, although tolerated in some patients
- >2.5 µcg/L: gastro-intestinal, cardiovascular system and central nervous system toxicity.

Distribution

Digoxin is widely distributed and extensively bound in varying degrees to tissues throughout the body. This results in a high apparent volume of distribution. Digoxin volume of distribution can be estimated using the equation 7.3 L/kg (ideal body weight (BWt)) which is derived from population data. However, distribution is altered in patients with renal impairment, and a more accurate estimate in these patients is given by:

$$V_d = 3.8 \times \text{ideal BWt} + (3.1 \times \text{creatinine clearance (mL/min)})$$

A two-compartment model best describes digoxin disposition (see Fig. 3.3), with a distribution time of 6–8 h. Clinical effects are seen earlier after intravenous doses, since the myocardium has a high blood perfusion and affinity for digoxin. Sampling for TDM must be done no sooner than 6 h post-dose, otherwise an erroneous result will be obtained.

Elimination

Digoxin is eliminated primarily by renal excretion of unchanged drug (60–80%), but some hepatic metabolism occurs (20–40%). The population average value for digoxin clearance is:

$$\text{digoxin clearance (mL/min)} = 0.8 \times \text{BWt} + (\text{creatinine clearance (mL/min)})$$

However, patients with severe congestive heart failure have a reduced hepatic metabolism and a slight reduction in renal excretion of digoxin:

$$\text{digoxin clearance (mL/min)} = 0.33 \times \text{BWt} + (0.9 \times \text{creatinine clearance (mL/min)})$$

Ideal body weight should be used in these equations.

Absorption

Digoxin is poorly absorbed from the gastro-intestinal tract, and dissolution time affects the overall bioavailability. The two oral formulations of digoxin have different bioavailabilities:

$$F(\text{tablets}) = 0.65$$

$$F(\text{liquid}) = 0.8$$

Practical implications

Using population averages it is possible to predict plasma concentrations from specific dosages, particularly since the time to reach the steady state is long. Population values are only averages, and individual values may vary. In addition, a number of diseases and drugs affect digoxin disposition.

As can be seen from the preceding discussion, congestive heart failure, hepatic and renal diseases all decrease the elimination of digoxin. In addition, hypothyroidism increases the plasma concentration (decreased metabolism and renal excretion) and increases the sensitivity of the heart to digoxin. Hyperthyroidism has the opposite effect. Hypokalaemia, hypercalcaemia, hypomagnesaemia and hypoxia all increase the sensitivity of the heart to digoxin. There are numerous drug interactions reported of varying clinical significance. The usual cause is either altered absorption or clearance.

Theophylline

Theophylline is an alkaloid related to caffeine. It has a variety of clinical effects including mild diuresis, central nervous system stimulation, cerebrovascular vasodilatation, increased cardiac output and bronchodilatation. It is the last which is the major therapeutic effect of theophylline. Theophylline does have some serious toxic effects. However, there is a good plasma concentration–response relationship.

Plasma concentration–response relationship

- <5 mg/L: no bronchodilatation[1]
- 5–10 mg/L: some bronchodilatation and possible anti-inflammatory action
- 10–20 mg/L: optimum bronchodilatation, minimum side effects
- 20–30 mg/L: increased incidence of nausea, vomiting[2] and cardiac arrhythmias
- >30 mg/L: cardiac arrhythmias, seizures.

Distribution

Theophylline is extensively distributed throughout the body, with an average volume of distribution based on population data of 0.48 L/kg.

Theophylline does not distribute very well into fat, and estimations should be based on ideal body weight. A two-compartment model best describes theophylline disposition, with a distribution time of approximately 40 min.

Elimination

Elimination is a first-order process primarily by hepatic metabolism to relatively inactive metabolites.

The population average for theophylline clearance is 0.04 L/h/kg, but this is affected by a number of diseases/drugs/pollutants. Therefore, this value should be multiplied by:

- 0.5 where there is cirrhosis, or when cimetidine, erythromycin or ciprofloxacin are being taken concurrently due to enzyme inhibition in the liver;
- 0.4 where there is congestive heart failure with hepatomegaly due to reduced hepatic clearance;
- 0.8 where there is severe respiratory obstruction (FEV1 < 1 L);
- 1.6 for patients who smoke (defined as more than 10 cigarettes per day), since smoking stimulates hepatic metabolism of theophylline.

Neonates metabolise theophylline differently, with 50% being converted to caffeine. Therefore, when it is used to treat neonatal apnoea of prematurity, a lower therapeutic range is used (usually 5–10 mg/L), since caffeine contributes to the therapeutic response.

[1]Some patients exhibit a clinical effect at these levels which has been attributed to possible anti-inflammatory effects.
[2]Nausea and vomiting can occur within the therapeutic range.

Product formulation

Aminophylline (the ethylenediamine salt of theophylline) is only 80% theophylline. Therefore, the salt factor (*S*) is 0.8. Most sustained-release (SR) preparations show good bioavailability but not all SR preparations are the same, which is why advice in the BNF recommends patients are maintained on the same brand.

Practical implications

Intravenous bolus doses of aminophylline need to be given slowly (preferably by short infusion) to avoid side effects due to transiently high blood levels during the distribution phase. Oral doses with sustained release preparations can be estimated using population average pharmacokinetic values and titrated proportionately according to blood levels and clinical response. In most circumstances, sustained release preparations may be assumed to provide 12 h cover. However, more marked peaks and troughs are seen with fast metabolisers (smokers and children). In these cases, the sustained release preparation with the lowest k_a value may be used twice daily (e.g. Uniphyllin (k_a = 0.22)). Alternatively, thrice daily dosage is required if a standard (k_a = 0.3–0.4) sustained release product is used (e.g. Phyllocontin (k_a = 0.37) or Nuelin SA (k_a = 0.33)).

Gentamicin

Clinical use

The spectrum of activity of gentamicin is similar to other aminoglycosides but its most significant activity is against *Psuedomonas aeruginosa.* It is still regarded by many as first choice for this type of infection.

Therapeutic range

Gentamicin has a low therapeutic index, producing dose-related side effects of nephro- and ototoxicity. The use of TDM to aid dose adjustment is essential if these toxic effects which appear to be related to peak and trough plasma levels are to be avoided. It is generally accepted that the peak level (drawn 1 h post-dose after an intravenous bolus or intramuscular injection) should not exceed 12 mg/L and the trough level (drawn immediately pre-dose) should not exceed 2 mg/L.

The above recommendations relate to multiple daily dosing of gentamicin. If once daily dosing is used, then different monitoring and interpretation parameters apply as described at the end of this section.

Distribution

Gentamicin is relatively polar and distributes primarily into extracellular fluid. Thus, the apparent volume of distribution is only 0.3 L/kg. Gentamicin follows a two-compartment model with distribution being complete within 1 h.

Elimination

Elimination is by renal excretion of the unchanged drug. Gentamicin clearance is approximately equal to creatinine clearance.

Practical implications

Since the therapeutic range is based on peak (1 h post-dose to allow for distribution) and trough (pre-dose) concentrations, it is necessary to be able to predict these from any given dosage regimen.

Initial dosage. This may be based on the patient's physiological parameters. Gentamicin clearance may be determined directly from creatinine clearance. The volume of distribution may be determined from ideal body weight. The elimination constant k_e may then be estimated using these parameters in Eq. (6). By substituting k_e and the desired peak and trough levels into Eq. (7), the optimum dosage interval can be determined (add on 1 h to this value to account for sampling time). Using this value (or the nearest practical value) and the desired peak or trough value substituted into Eq. (13) or Eq. (14), it is possible to determine the appropriate dose.

Changing dosage. This is not as straightforward as for theophylline or digoxin, since increasing the dose will increase the peak and trough levels proportionately. If this is not desired, then use of pharmacokinetic equations is necessary. By substituting the measured peak and trough levels and the time between them into Eq. (7), it is possible to determine k_e (and the half-life from Eq. (8) if required). To estimate the patient's volume of distribution from actual blood level data, it is necessary to know the C^{ss}_{max} immediately after the dose (time zero), not the 1 h value which is measured. To obtain this, Eq. (7) may be used, this time substituting the trough level for C_2 and solving for C_1. Subtracting the trough level from this C^{ss}_{max} at time zero, the volume of distribution may be determined from Eq. (10). Using these values for k_e and V_d, derived from actual blood level data, a new dose and dose interval can be determined as before.

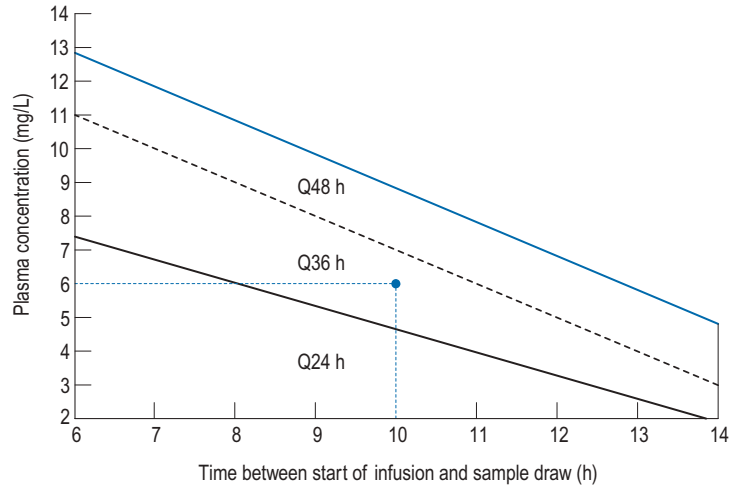
Once daily dosing. There are theoretical arguments for once daily dosing of gentamicin, since aminoglycosides display concentration-dependent bacterial killing, and a high enough concentration to minimum inhibitory concentration (MIC) ratio may not be achieved with multiple dosing. Furthermore, aminoglycosides have a long post-antibiotic effect. Aminoglycosides also accumulate in the kidneys, and once daily dosing could reduce renal tissue accumulation. There have been a number of clinical trials comparing once daily administration of aminoglycosides with conventional administration. A small number of these trials have shown less nephrotoxicity, no difference in ototoxicity, and similar efficacy with once daily administration.

Initial dosage for a once daily regimen is 5–7 mg/kg/day for patients with a creatinine clearance of >60 mL/min. This is subsequently adjusted on the basis of blood levels. However, monitoring of once daily dosing of gentamicin is different to multiple dosing. One approach is to take a blood sample 6–14 h after the first dose and plot the time and result on a standard concentration-time plot (the Hartford nomogram, Nicolau et al., 1995; Fig. 3.7). The position of the individual patient's point in relation to standard lines on the nomogram indicates what the most appropriate dose interval should be (either 24, 36 or 48 h). Once daily dosing of gentamicin has not been well studied in pregnant or breastfeeding women, patients with major burns, renal failure, endocarditis or cystic

If result available within 24 h

- Use graph below to select dose interval. Use serum concentration and time interval between start of infusion and sample to plot intercept (see example given on graph).
- Give next dose (7 mg/kg by infusion as above) after interval indicated by graph.
  If result falls above upper limit for Q48 h, abandon once daily regimen. Measure gentamicin concentration after another 24 h and adopt multiple daily dose regimen if result <2 mg/L
  If result falls on Q24 h sector it is not necessary to recheck gentamicin concentration within 5 days unless patient's condition suggests renal function may be compromised.

- **Graph:** Use values of plasma concentration and time interval to find intercept (Example given of 6 mg/L after 10 h yields dose interval of 36 h)



MONITORING

- Repeat U&E daily. Calculate creatinine clearance from serum creatinine to check dose interval has not changed.
- If dose interval has to be changed, check gentamicin concentration 6 – 14 h after start of next infusion note time of start of infusion and time of sampling and use graph to verify correct dose interval.

Fig. 3.7 Nomogram for adjustment of once daily gentamicin dosage (Nicolau et al., 1995).

fibrosis. Therefore, it cannot be recommended in these groups and multiple daily dosing should be used.

Lithium

Lithium is effective in the treatment of acute mania and in the prophylaxis of manic depression. The mechanism of action is not fully understood, but it is thought that it may substitute for sodium or potassium in the central nervous system. Lithium is toxic, producing dose-dependent and dose-independent side effects. Therefore, TDM is essential in assisting in the management of the dosage.

Dose-dependent effects

The plasma concentration–response relationship derived on the basis of the 12-h standardised lithium level (measured 12 h after the evening dose of lithium) is shown below:

- <0.4 mmol/L: little therapeutic effect
- 0.4–1.0 mmol/L: optimum range for prophylaxis
- 0.8–1.2 mmol/l: optimum range for acute mania
- 1.2–1.5 mmol/L: causes possible renal impairment
- 1.5–3.0 mmol/L: causes renal impairment, ataxia, weakness, drowsiness, thirst, diarrhoea
- 3.0–5.0 mmol/L: causes confusion, spasticity, dehydration, convulsions, coma, death. (Levels above 3.5 mmol/L are regarded as a medical emergency.)

Dose-independent effects

These include tremor, hypothyroidism (approximately 10% of patients on chronic therapy), nephrogenic diabetes insipidus, gastro-intestinal upset, loss in bone density, weight gain (approximately 20% of patients gain more than 10 kg) and lethargy.

Distribution

Lithium is unevenly distributed throughout the body, with a volume of distribution of approximately 0.7 L/kg. Lithium follows a two-compartment model (see Fig. 3.3) with a distribution time of 8 h (hence, the 12-h sampling criterion).

Elimination

Lithium is excreted unchanged by the kidneys. Lithium clearance is approximately 25% of creatinine clearance, since there is extensive reabsorption in the renal tubules.

In addition to changes in renal function, dehydration, diuretics (particularly thiazides), angiotensin-converting enzyme inhibitors (ACE inhibitors) and non-steroidal anti-inflammatory drugs (NSAIDs) (except aspirin and sulindac) all decrease lithium clearance. Conversely, aminophylline and sodium loading increase lithium clearance.

Notwithstanding the above factors, there is a wide inter-individual variation in clearance, and the lithium half-life in the population varies between 8 and 35 h with an average of approximately 18 h. Lithium clearance shows a diurnal variation, being slower at night than during the day.

Practical implications

In view of the narrow therapeutic index, lithium should not be prescribed unless facilities for monitoring plasma lithium concentrations are available. Since lithium excretion is a first-order process, changes in dosage result in a proportional change in blood levels. Blood samples should be drawn 12 h after the evening dose, since this will allow for distribution and represent the slowest excretion rate. Population pharmacokinetic data (particularly the volume of distribution) cannot be relied upon to make initial dosage predictions, although renal function may give an approximate guide to clearance. Blood level measurements are reported in SI units and therefore it is useful to know the conversion factors for the various salts.

- 100 mg of lithium carbonate is equivalent to 2.7 mmol of lithium ions
- 100 mg of lithium citrate is equivalent to 1.1 mmol of lithium ions.

Phenytoin

Phenytoin is used in the treatment of epilepsy (see Chapter 31). Use is associated with dose-independent side effects which include hirsutism, acne, coarsening of facial features, gingival hyperplasia, hypocalcaemia and folic acid deficiency. However, phenytoin has a narrow therapeutic index and has serious concentration-related side effects.

Plasma concentration–response relationship

- <5 mg/L: generally no therapeutic effect
- 5–10 mg/L: some anticonvulsant action with approximately 50% of patients obtaining a therapeutic effect with concentrations of 8–10 mg/L
- 10–20 mg/L: optimum concentration for anticonvulsant effect
- 20–30 mg/L: nystagmus, blurred vision
- >30 mg/L: ataxia, dysarthria, drowsiness, coma.

Distribution

Phenytoin follows a two-compartment model with a distribution time of 30–60 min. The apparent volume of distribution is 1 L/kg.

Elimination

The main route of elimination is via hepatic metabolism. However, this metabolic route can be saturated at normal therapeutic doses. This results in the characteristic non-linear dose/concentration curve seen in Fig. 3.6B. Therefore, instead of the usual first-order pharmacokinetic model, a Michaelis–Menten model, used to describe enzyme activity, is more appropriate.

Using this model, the daily dosage of phenytoin can be described by

$$\frac{S \times F \times \text{dose}}{T} = \frac{V_{max} \times C^{ss}}{K_m + C^{ss}} \quad (15)$$

K_m is the plasma concentration at which metabolism proceeds at half the maximal rate. The population average for this is 5.7 mg/L, although this value varies greatly with age and race.

V_{max} is the maximum rate of metabolism of phenytoin and is more predictable at approximately 7 mg/kg/day.

Since clearance changes with blood concentration, the half-life also changes. The usual reported value is 22 h, but this increases as concentration increases. Therefore, it is difficult to predict when the steady state will be reached. However, as a rule of thumb, 1–2 weeks should be allowed to elapse before sampling after a dosage change.

In overdose, it can be assumed that metabolism of the drug is occurring at the maximum rate of V_{max}. Therefore, the decline in plasma concentration is linear (zero-order) at approximately 7 mg/L/day.

Practical implications

Since the dose/concentration relationship is non-linear, changes in dose do not result in proportional changes in plasma concentration (see Fig. 3.6B). Using the Michaelis–Menten model, if the plasma concentration is known at one dosage, then V_{max} may be assumed to be the population average (7 mg/kg/day), since this is the more predictable parameter, and K_m calculated using Eq. (15). The revised values of K_m can then be used in Eq. (15) to estimate the new dosage required to produce a desired concentration. Alternatively, a nomogram may be used to assist in dose adjustments (Fig. 3.8).

Care is needed when interpreting TDM data and making dosage adjustments when phenytoin is given concurrently with other anticonvulsants, since these affect distribution and metabolism of phenytoin. Since phenytoin is approximately 90% protein bound, in patients with a low plasma albumin and or uraemia, the free fraction increases and therefore an adjusted total phenytoin should be calculated or a free salivary level taken. To adjust the observed concentration in hypoalbuminaemia the following equation can be applied:

$$C_{adjusted} = \frac{C_{observed}}{0.9 \times (C_{albumin} / 44) + 0.1}$$

Albumin concentration is in g/L.

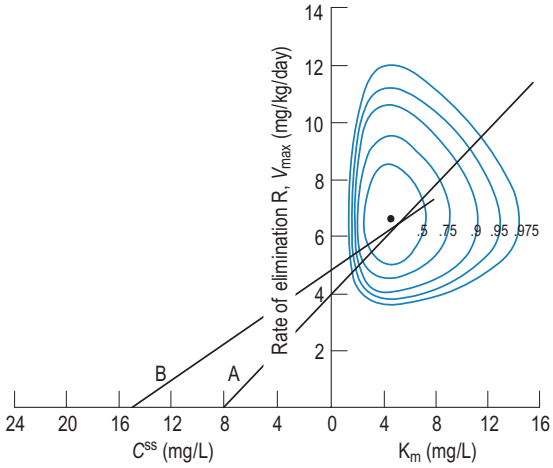


Fig. 3.8 Orbit graph. The most probable values of V_{max} and k_m for a patient may be estimated using a single steady-state phenytoin concentration and a known dosing regimen. The eccentric circles or 'orbits' represent the fraction of the sample patient population whose k_m and V_{max} values are within that orbit. (1) Plot the daily dose of phenytoin (mg/kg/day) on the vertical line (rate of elimination). (2) Plot the steady-state concentration (C^{ss}) on the horizontal line. (3) Draw a straight line connecting C^{ss} and daily dose through the orbits (line A). (4) The coordinates of the mid point of the line crossing the innermost orbit through which the line passes are the most probable values for the patient's V_{max} and k_m. (5) To calculate a new maintenance dose, draw a line from the point determined in Step 4 to the new desired C^{ss} (line B). The point at which line B crosses the vertical line (rate of elimination) is the new maintenance dose (mg/kg/day). The line A represents a C^{ss} of 8 mg/l on 276 mg/day of phenytoin acid (300 mg/day of sodium phenytoin) for a 70 kg patient. Line B has been drawn assuming the new desired steady-state concentration was 15 mg/L (μg/mL). The original figure is modified so that R and V_{max} are in mg/kg/day of phenytoin acid (modified from Evans et al., 1992).

In ureamic patients with severe renal failure, the unbound fraction is approximately doubled, so the target concentration needs to be half the normal concentration or apply the adjusted concentration equation if albumin level is known.

The oral formulations of phenytoin show good bioavailability. However, tablets and capsules contain the sodium salt (S = 0.9), whereas the suspension and infatabs are phenytoin base (S = 1). Intramuscular phenytoin is slowly and unpredictably absorbed, due to crystallisation in the muscle tissue, and is therefore not recommended. Fosphenytoin, a prodrug of phenytoin, is better absorbed from the intramuscular site. Doses should be expressed as phenytoin equivalent. Fosphenytoin sodium 1.5 mg is equivalent to phenytoin sodium 1 mg.

Carbamazepine

Carbamazepine is indicated for the treatment of partial and secondary generalised tonic-clonic seizures, primary generalised tonic-clonic seizures, trigeminal neuralgia, and prophylaxis of bipolar disorder unresponsive to lithium. There are a number of dose-independent side effects, including various dermatological reactions and, more rarely, aplastic anaemia and Stevens–Johnson syndrome. However, the more common side effects are concentration related.

Plasma concentration–response relationship when used in the treatment of epilepsy

- <4 mg/L: little therapeutic benefit
- 4–12 mg/L: optimum therapeutic range for monotherapy
- >9 mg/L: possible side effects of nystagmus, diplopia, drowsiness and ataxia, particularly if patients are on other anticonvulsant therapy
- >12 mg/L: side effects common, even on monotherapy.

Distribution

Carbamazepine is distributed widely in various organs, with the highest concentration found in liver and kidneys. Carbamazepine is 70–80% protein bound and shows a wide variation in the population average apparent volume of distribution (0.8–1.9 L/kg). This wide variation is thought to be due to variations in absorption (since there is no parenteral form) and protein binding.

Elimination

Carbamazepine is eliminated almost exclusively by metabolism, with less than 2% being excreted unchanged in the urine. Elimination is a first-order process, but carbamazepine induces its own metabolism (auto-induction). Therefore, at the beginning of therapy, clearance is 0.01–0.03 L/h/kg, rising to 0.05–0.1 L/h/kg on chronic therapy. Auto-induction begins in the first few days of commencing therapy and is maximal at 2–4 weeks.

Since clearance changes with time, so does half-life, with reported values as long as 35 h after a single dose, decreasing to 5–7 h on regular dosing.

Absorption

Absorption after oral administration is slow, with peak concentrations being reached 2–24 h post-dose (average 6 h). Absorption is incomplete, with bioavailability estimated at approximately 80% (F = 0.8).

Practical implications

Use of pharmacokinetic equations is limited, due to the auto-induction effect. However, there are a number of important practical points:

- Blood samples should not be drawn before the steady state, which will not be achieved until 2–4 weeks after starting therapy to allow for auto-induction, or 3–4 days after subsequent dose adjustments.
- When sampling, the trough level should be measured because of the variable absorption pattern.
- Complex calculations are not helpful, but as a rule of thumb each 100 mg dose will increase the plasma concentration at the steady state by approximately 1 mg/L in adults.

- A number of other drugs (including phenytoin) when given concurrently will affect carbamazepine metabolism and subsequent blood levels.

Phenobarbital

Phenobarbital is indicated in all forms of epilepsy except absence seizures. Although there is a clear concentration–response relationship, routine plasma concentration monitoring is less useful than for other drugs, since tolerance occurs.

Plasma concentration–response relationship

- <15 mg/L: little therapeutic effect
- 15–40 mg/L: optimum range
- 40–50 mg/L: sedation, confusion (elderly), although may be tolerated by some patients
- >60 mg/L: serious toxic effect of ataxia, lethargy, stupor, coma.

The sedation which commonly manifests early on in therapy becomes less with continued therapy.

Distribution

Phenobarbital readily distributes into most body tissues and is 50% protein bound. The population-average volume of distribution is 0.7–1 L/kg.

Elimination

Phenobarbital is primarily (80%) metabolised by the liver, with approximately 20% being excreted unchanged in the urine. Elimination is a first-order process, but is relatively slow with a population average clearance of approximately 0.004 L/h/kg. However, as with theophylline, clearance in children is increased and is approximately twice the adult clearance. Applying Eqs. (6) and (8) to these population values gives an estimate of the half-life of the order of 5 days. This is much shorter in children and longer in the elderly.

Practical application

In view of the long half-life, single daily dosage is possible with phenobarbital. Samples for therapeutic monitoring may be drawn any time during a dose interval, since concentration fluctuation between doses is minimal. However, the patient should be at the steady state, which takes 2–4 weeks (1–2 weeks in children). The pharmacokinetics of phenobarbital may be altered by liver and (less markedly) renal disease, but are not affected by the concurrent administration of other anticonvulsants.

Primidone

Like phenobarbital, primidone is effective in the treatment of tonic–clonic and partial seizures. Much of the anticonvulsant activity of primidone is due to the metabolites phenobarbital and phenylethylmalonamide. Therefore, primidone plasma concentrations are only useful to confirm transient toxicity. Toxic manifestations such as sedation, nausea and ataxia are seen at concentrations greater than 15 mg/L. The plasma concentration should be drawn approximately 3 h post dose, which corresponds to the peak concentration.

Phenylethylmalonamide assays are not routinely available, although this metabolite probably contributes to anticonvulsant activity. Measurement of phenobarbital levels is of limited value, since conversion of primidone to phenobarbital is variable between individuals. However, phenobarbital levels may be helpful in dosage selection, where seizures are not adequately controlled despite regular dosage, or where there is suspected toxicity.

Valproate

Sodium valproate as valproic acid in the bloodstream has a broad spectrum of anticonvulsant activity, being useful in generalised absence, generalised tonic–colonic and partial seizures.

Plasma concentration–response relationship

There is no clear concentration–response relationship for valproate, although a range of 50–100 mg/L is often quoted as being optimal, with 50% of patients showing a response at levels above 80 mg/L. Levels above 100 mg/L do not confer any additional therapeutic benefits. Although there is no clear relationship between plasma levels and toxic effects, the rare hepatotoxicity associated with valproate appears to be related to very high levels of over 150 mg/L.

Distribution

Valproate is extensively bound to plasma protein (90–95%), and unlike other drugs, it can saturate protein binding sites at concentrations greater than 50 mg/L, altering the free fraction of drug. Therefore, the apparent volume of distribution of valproate varies from 0.1 to 0.5 L/kg.

Elimination

Elimination of valproate is almost entirely by hepatic metabolism, with less than 5% being eliminated by the kidneys.

As a result of the saturation of protein binding sites and the subsequent increase in the free fraction of the drug, clearance of the drug increases at higher concentrations. Therefore, there is a non-linear change in plasma concentration with dose (illustrated in Fig. 3.6C).

Practical implications

In view of the lack of a clear concentration–response relationship and the variable pharmacokinetics, there are limited indications for the measurement of valproate levels. In most cases, dosage should be based on clinical response. Valproic acid can take several weeks to become fully active, so adjustment of doses must not be made quickly.

In a few cases where seizures are not controlled at high dosage, a plasma level may be helpful in confirming treatment failure. If monitoring is to be undertaken, levels should be drawn at steady state (2–3 days). A trough sample will be the most useful, since wide fluctuations of blood levels may occur during a dose interval.

Lamotrigine, vigabatrin, gabapentin, tiagabine, topiramate, pregabalin, lacosamide and levetiracetam

These newer medicines are indicated for the treatment of a range of types of epilepsy and some with additional indications. All are used as adjunctive treatment with other anticonvulsants, and some indicated for monotherapy.

Plasma concentration–response relationship

There is no clear relationship between plasma concentration and response for these newer anticonvulsants. The situation is further complicated by the fact that these preparations are usually used as add-on therapy with other anticonvulsants.

Practical implications

While these newer anticonvulsants have narrow therapeutic indices and inter- and intra-individual variation in pharmacokinetics, there is not enough evidence to support routine TDM, and dosage should be titrated to clinical response.

Ciclosporin

Ciclosporin is a neutral lipophilic cyclic endecapeptide extracted from the fungus *Tolypocladium inflatum gams*. It is a potent immunosuppressive agent, used principally to reduce graft rejection after organ and tissue transplantation. The drug has a low therapeutic index, with a number of toxic effects including nephrotoxicity, hepatotoxicity, gastro-intestinal intolerance, hypertrichosis and neurological problems. Efficacy in reducing graft rejection as well as the main toxic effect of nephro- and hepatotoxicity appear to be concentration related.

Plasma concentration–response relationship

With all drugs that are monitored the therapeutic range is a window with limits, which are not absolute. It is even more difficult to define a therapeutic range for ciclosporin, since there are a number of influencing factors. First, the measured concentration varies depending on sampling matrix (i.e. whole blood or plasma). Second, it depends on whether the assay is specific for ciclosporin alone or non-specific to include metabolites. A target concentration varies between centres, but is commonly around 100–200 ng/mL in the first 6 months after transplantation and 80–150 ng/mL from 6 months onwards. Levels below the lower limit of this window are associated with an increased incidence of graft rejection. Levels above the upper limit are associated with an increased incidence of nephrotoxicity and hepatotoxicity.

Distribution

Ciclosporin is highly lipophilic and is distributed widely throughout the body with a volume of distribution of 4–8 L/kg. There is variable distribution of ciclosporin within blood, since the whole blood concentration is approximately twice the plasma concentration. Within plasma, ciclosporin is 98% protein bound.

Elimination

Ciclosporin is eliminated primarily by hepatic metabolism, with wide inter-individual variation in clearance (0.1–2 L/h/kg). In children these values are approximately 40% higher, with a resulting increased dosage requirement on a milligram per kilogram basis. In elderly patients or patients with hepatic impairment a lower clearance rate has been observed.

Practical implications

In addition to the wide inter-patient variability in distribution and elimination pharmacokinetic parameters, absorption of standard formulations of ciclosporin is variable and incomplete (F = 0.2–0.5 in normal subjects). In transplant patients this variation in bioavailability is even greater, and increases during the first few months after transplant. Furthermore, a number of drugs are known to interact with ciclosporin. All these factors suggest that therapeutic drug monitoring will assist in optimum dose selection, but the use of population averages in dose prediction is of little benefit, due to wide inter-patient variation. When using TDM with ciclosporin a number of practical points need to be considered:

- The sampling matrix should be whole blood, since there is a variable distribution of ciclosporin between blood and plasma.
- Samples should represent trough levels and be drawn at the steady state, which is achieved 2–3 days after initiating or changing the dosage (average half-life is 9 h).
- Ciclosporin concentration monitoring should be undertaken every 2–3 days in the immediate postoperative phase until the patient's clinical condition is stable. Thereafter, monitoring can be undertaken every 1–2 months.
- TDM should be performed when changing brands of ciclosporin, since there are marked differences in the bioavailability of different brands.

Summary pharmacokinetic data for drugs with therapeutic plasma concentrations are listed in Table 3.1.

Table 3.1 Summary of pharmacokinetic data

Drug	Therapeutic range of plasma concentrations	V_d (L/kg)	CL (L/h/kg)	Half-life (h)
Digoxin	0.8–2.0 µcg/L (0.5–0.9 µcg/L in patients >65) 1–2.6 nmol/L (0.625 nmol/L – 1.1 nmol/L in patients >65)	7.3	See text	36
Theophylline	10–20 mg/L 55–110 µmol/L	0.48	0.04	8
Gentamicin	Peak 5–12 mg/L, trough <2 mg/L	0.3	1 × CL (creatinine)	2
Lithium	0.4–0.8 mmol/L	0.5–1	0.2 × CL (creatinine)	18
Phenytoin	10–20 mg/L 40–80 µmol/L	1	K_m = 5.7 mg/L V_{max} = 7 mg/kg/day	
Carbamazepine	4–12 mg/L 17–50 µmol/L	0.8–1.9	0.05–1	
Phenobarbital	15–40 mg/L 65–172 µmol/L	0.7–1	0.004	120
Primidone	<15 mg/L <69 µmol/L	0.6		
Valproate	<100 mg/L <693 µmol/L			
Ciclosporin	Varies between centres 100–200 ng/mL (first 6 months after transplantation) 80–150 ng/mL (from 6 months onwards)			9

Population pharmacokinetic parameters are based on averages. The degree of variability around the average is different for each drug. See text for variability.

Case studies

Case 3.1

You are reviewing a formulary submission for a new formulation of a product, which has reportedly an improved side effect profile due to better absorption characteristics. However, there is conflicting evidence in the literature over the absorption of the new preparation. One paper, which is available to you, shows a concentration-time profile for the oral formulation after a single oral dose of 250 mg as in Table 3.2.

The paper also quotes an area under the curve (AUC) after a single i.v. dose of 200 mg as 87 mg/L/h.

Table 3.2 Concentration-time profile for the oral formulation after a single oral dose of 250 mg

Time after administration	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	9 h	10 h	11 h	12 h
Concentration (mg/L)	10	18	12.7	9	6.4	4.5	3.2	2.25	1.6	1.1	0.78	0.55

Questions

1. What is the AUC after the single oral dose of 250 mg?
2. What is the bioavailability of the new formulation?

Answers

1. Draw the concentration-time profile on a piece of paper; try to do it reasonably accurately but it does not have to be exact. Draw down vertical lines from the curve at each 1-h time interval to create a series of trapeziums (the first one is actually a triangle). Calculate the area of each trapezium from the formula

   Area of trapezium = (sum of the height of each side/2) × width (1h)

   Then add all the areas together (assume a value of 0 after 12 h)

   AUC p.o. = 69.99 mg/L/h

2. From the equation $F = \frac{\text{D i.v.} \times \text{AUC p.o.}}{\text{D p.o.} \times \text{AUC i.v.}}$

   $F = 200 \times 69.99 / 250 \times 87$

   $F = 0.64$

Case 3.2

An 86-year-old lady is admitted to hospital by her primary care doctor, with increasing shortness of breath. She lives alone, is independent and has a flat on the 5th floor of a block of flats. She has a stable plasma creatinine of 150 μmol/L

She is 55 kg, 4′ 11″ tall.

She is known to have recently diagnosed atrial fibrillation, osteoporosis and ischaemic heart disease.

Her current medication is:

Aspirin	**300 mg daily**
Adcal D3	**Two tablets daily**
Imdur	**60 mg daily**
Simvastatin	**40 mg daily**
Senna	**7.5 mg daily**
Digoxin	**62.5 μcg daily**

She has been taking digoxin in a dose of 62.5 μcg daily for the last 3 weeks.

Questions

1. Calculate the predicted digoxin level for this lady.
2. A digoxin blood level is reported to be 1.0 μcg/L. List the reasons for the difference between the measured and predicted digoxin levels.
3. The hospital doctor queries if he should increase the dose of digoxin as the blood level is on the low side. Use an evidence-based approach to reply to the clinician.

Answers

1. Her predicted glomerular filtration rate is calculated from Cockcroft-Gault equation:

$$\text{Creatinine clearance (mL/min)} = \frac{F \times [(140 - \text{age in years}) \times \text{weight (kg)}]}{\text{plasma creatinine (μmol/L)}}$$

$$\text{Creatinine clearance } (CL_{cr}) = \frac{1.04(140 - 86)55}{150} = 20.6 \text{ mL/min}$$

On the assumption that the patient has severe congestive heart failure, the predicted digoxin level is calculated using the equation:

$$CL_{dig} = 0.33 \times IBW + 0.9 \times CL_{cr}$$
$$= (0.33 \times 55) + (0.9 \times 20.6) = 36.69 \text{ mL/min} = 2.2 \text{ L/h}$$

Ideal body weight (IBW (kg)):

$$\text{Male} = 50 + (2.3 \times \text{height in inches over 5 feet})$$

$$\text{Female} = 45.5 + (2.3 \times \text{height in inches over 5 feet})$$

Equation (4) rate of administration = rate of elimination = $CL \times C^{ss}$

Rearranging Eq. (4):

$$C_{ssave} = \frac{\text{Dose} \times S \times F}{CL_{dig} \times \tau} = \frac{62.5 \times 1 \times 0.63}{2.2 \times 2.4} = 0.75 \text{ μcg/L}$$

2. The predicted level is less than the measured level, this may be because:
   - The level has been taken less than 6 h after the oral dose
   - Suspected non-adherence
   - Congestive heart failure has affected the renal function
3. A subgroup analysis of the Digitalis Investigation Group suggested that participants >65 years who had low blood levels (0.5–0.9 μcg/L) had reductions in all – cause mortality. It has also been suggested that digoxin may be associated with an increased risk of problems in patients with atrial fibrillation (Gjesdal et al., 2008). Therefore, the dose of digoxin should not be increased.

Case 3.3

A 68-year-old man (72 kg, 5′ 2″ tall) is admitted to the medical ward from intensive care as he is in a stable condition. He was admitted 2 days ago with Gram negative sepsis identified from a blood culture. He was commenced on gentamicin 5 mg/kg once daily as per the hospital protocol.

Current laboratory results are:

Urea	**31.6 mmol/L (3.2–7.5 mmol/L)**
Creatinine	**168 μmol/L (71–133 μmol/L)**

Gentamicin levels were taken 1 and 8 h after the first dose and reported as 19 and 10 mg/L, respectively.

Questions

1. Calculate the patient's elimination constant k_e.
2. Calculate the plasma concentration at C^o immediately after the injection.
3. Using the plasma concentration at C^o calculate the level you would expect the patient to achieve immediately prior to his next dose.
4. Calculate the dosage interval you would recommend aiming for a trough of 1 mg/L.

Answers

1. As the two plasma levels are known the elimination constant k_e is calculated from the following equation.

$$k_e = \frac{\ln C_1 - \ln C_2}{t}$$

Using the plasma levels reported:

$$k_e = \frac{\ln 19 - \ln 10}{7}$$

$$k_e = 0.092 \text{ h}^{-1}$$

2. The plasma concentration at C^o immediately after the injection is calculated as:

$$C^t = C^o \times e^{-k_e \times t}$$

$$19 = C^o \times e^{-0.092 \times 1}$$

$$C^o = 20.8 \text{ mg/L}$$

3. The plasma concentration at C^o is then used to calculate the expected level to be achieved immediately prior to his next dose.

$$C^t = C^o \times e^{-k_e \times t}$$

$$C^t = 20.8 \times e^{-0.092 \times 24}$$

$$= 2.2 \text{ mg/L}$$

4. The dosage interval can then be calculated for a trough of 0.5 mg/L

$$Cp^t = Cp^o \times e^{-k_e \times t}$$

$$\ln 0.5 = \ln 20.8 \times (-0.092 \times t)$$

$$-0.693 = 3.03 \times (-0.092 \times t)$$

$$t = 40.52 \text{ h}$$

As this time interval is more than 24 h and could potentially become nephrotoxic/ototoxic, an alternative antibiotic should be prescribed.

Case 3.4

A 68-year-old Argentinean man (69 kg) was found wandering in the street. A neighbour alerted the police. He was described as being confused and agitated. The patient could not speak English and on admission to hospital could not give a history. The neighbour told the ambulance staff the patient was normally well, but known to be taking medicines for a mental disorder. The ambulance staff found lithium and amisulpride in the man's pockets.

A sample of lithium was taken and reported as 2.5 mmol/L (0.6–1 mmol/L). His plasma creatinine was 160 µmol/L so the lithium was stopped.

Questions

1. Calculate the patient's pharmacokinetic parameters clearance (CL), volume of distribution (V_d), elimination constant (k_e) using population data.
2. Estimate the time for the lithium level to decrease to the middle of the normal range.
3. Briefly describe the symptoms of lithium toxicity.

Answers

1. Population data suggests that the clearance of lithium can be calculated using the following equation:

$$\text{Clearance} = 0.25 \times \text{CrCL (L/h)}$$

The patient's creatinine clearance (CrCL) is calculated using the Cockcroft and Gault equation:

$$\text{Creatinine clearance (CrCL)} = \frac{1.23 \times (140 - \text{age}) \times \text{weight in kg}}{\text{Plasma creatinine (µmol/L)}}$$

$$\text{Creatinine clearance (CrCL)} = \frac{1.23 \times (140 - 68) \times 69}{160} = 38.2 \text{ mL/min}$$

Convert 38.2 mL/min to L/h

$$\frac{38.2 \times 60}{1000} = 2.29 \text{ L/h}$$

$$\text{Lithium clearance} = 0.25 \times 2.29 = 0.573 \text{ L/h}$$

Population data suggests that the volume of distribution (V_d) for lithium is 0.7 L/Kg.

Therefore, for this patient the volume of distribution:

$$V_d = 0.7 \times 69$$

$$V_d = 48.3 \text{ L}$$

The elimination rate constant k_e is calculated:

$$CL = k_e \times V_d \quad \text{to give } k_e = \frac{CL}{V_d}$$

$$k_e = \frac{0.573}{48.3}$$

$$k_e = 0.01186 \text{ h}^{-1}$$

2. The time it will take for this man's lithium level to return to the middle of the normal range (0.6-1 mmol/L), that is, 0.7 mmol/L is calculated using:

$$\text{Time to decay} = \frac{\ln Cp^1 - \ln Cp^2}{k_e}$$

$$\text{Time to decay} = \frac{\ln 2.5 - \ln 0.7}{0.01186}$$

$$\text{Time to decay} = 107.3 \text{ h} = 4.5 \text{ days}$$

3. Acute lithium toxicity tends to present with gastro-intestinal symptoms. If the toxicity is due to an increase in dose, symptoms will include neuromuscular signs, for example, ataxia and tremor. This is sometimes referred to as acute on chronic toxicity. Chronic toxicity is harder to treat due to tissue deposition and involves neurological problems.

Case 3.5

Mr B is a 38-year old, 63 kg man who suffers from asthma. He has been admitted to hospital and Nuelin S.A. 500 mg 12 hourly (6 am and 6 pm) has been added to his regimen. He responds well to this treatment but unfortunately after 2 days of treatment two doses are missed (evening dose and following morning dose). The clinical team is anxious to discharge him, so it is decided to give him a loading dose of aminophylline at 10 am before restarting him on maintainence therapy.

Questions

1. Was the patient at steady state before the medication was omitted?
2. What is the estimated theophylline level at 10 am?
3. The levels were then checked and the theophylline level was reported as 4 mg/L. What loading dose of i.v. aminophylline would you recommend?

Answers

1. His pharmacokinetic parameters can be calculated from population data

$$\text{Clearance} = 63 \text{ kg} \times 0.04 \text{ L/h/kg} = 2.52 \text{ L/h}$$

$$V_d = 63 \text{ kg} \times 0.45 \text{ L/kg} = 28.3 \text{ L}$$

$$k_e = \frac{CL}{V_d}$$

$$k_e = 0.089\ h^{-1}$$

Using Eq. (8), $t_{½} = 0.693/k_e$

The patient's half-life ($t_{1/2}$) = 7.8 h.
It can therefore be assumed he was at steady state after 48 h of treatment (more than 5 x half-life).

2. To calculate his levels at 10 am it is assumed that S.R. theophylline behaves like an i.v. infusion (F = 1.0). Although this is not strictly true, Nuelin S.A. has a good slow release profile.
From Eq. (12)

$$\frac{S \times F \times \text{dose}}{T} = \text{Average } C^{ss} \times \text{CL}$$

$$\text{Average } C^{ss} = \frac{S \times F \times \text{dose}}{T \times \text{CL}}$$

$$\text{Average } C^{ss} = \frac{500 \times 1}{12 \times 2.52}$$

$$\text{Average } C^{ss} = 16.5 \text{mg/L}$$

To calculate theophylline concentration at 10 am, $C^{10\ am}$ need to delay this for 16 h as the morning dose from the previous day will have provided a steady dose of theophylline until the evening (first missed dose), so starting dose is C^{ss}.
Using Eq. (7)

$$C_2 = C_1 \times e^{-k_e \times t}$$

$$C^{10\,am} = 16.5 \times e^{-k_e \times 16}$$

$$C^{10\,am} = 16.5 \times e^{-0.089 \times 16}$$

$$C^{10\,am} = 3.97 \text{mg/L}$$

3. To calculate a loading dose the change in theophylline concentration (C) to be achieved needs to be calculated:

$$C = \text{desired } C\ (15\ \text{mg/L}) - \text{actual}\ (4\ \text{mg/L})$$

From Eq. (1):

$$\text{Loading dose} = C \times V_d$$

$$\text{Loading dose} = 11 \times 28.3\ \text{L}$$

$$\text{Loading dose} = 311\ \text{mg of theophylline}$$

Aminophylline is only 80% theophylline, therefore

$$\text{Loading dose} = \frac{311}{0.8}$$

Aminophylline loading dose = 390 mg aminophylline to be administered by slow i.v. bolus.

Case 3.6

A 29-year-old man (70 kg) was diagnosed with TB meningitis 2 months ago. He is currently in hospital because of social issues. His liver function and other biochemical results are within the normal range. He was started on phenytoin capsules 350 mg daily at the time of diagnosis.

His current medication is:

Pyridoxine	**12.5 mg daily**
Rifater	**four tablets daily**
Phenytoin capsules	**350 mg daily**

One month after being started on this medication his phenytoin plasma level is measured as 7 mg/L

Questions

1. Using population data, calculate this man's predicted phenytoin plasma level.
2. Explain the difference between the predicted and actual phenytoin level
3. Using the phenytoin plasma level reported, assume steady state. Calculate this patient's V_{max}.
4. Calculate the dose required to obtain a plasma level of 10 mg/L at steady state.
5. Compare your answer using the orbit plot.

Answers

1. Using population data, calculate this man's predicted plasma level.
F, bioavailabilty; S, salt factor; V_{max}, maximum rate of metabolism; K_m, Michaelis-Menten constant.
V_{max} = 7 mg/kg/day, K_m = 5.7 mg/L, D = 350 mg, F = 1, S = 0.92.
Rearranging Eq. (15):

$$\frac{S \times F \times \text{dose}}{T} = \frac{V_{max} \times C^{ss}}{K_m + C^{ss}}$$

$$C^{ss} = \frac{K_m \times (S \times F \times \text{dose})}{(V_{max} \times T) - (S \times F \times \text{dose})}$$

$$C^{ss} = \frac{5.7 \times 0.92 \times 350}{70 \times 7 \times 1 - (0.92 \times 350)}$$

$$C^{ss} = \frac{1835.4}{490 - 322}$$

$$C^{ss} = 10.93\ \text{mg/L}$$

2. There are a number of potential reasons for the difference between the predicted and actual level:
   - The patient is not at steady state. This is unlikely as he has been on this medication from diagnosis 2 months ago.
   - The patient is not taking the phenytoin prescribed. This is also unlikely because as a hospital inpatient the nursing staff have been giving him his medication.
   - There is an interaction between the rifampacin and phenytoin. This is the most likely reason.
3. Using the plasma level reported, assume steady state. Calculate this patient's actual V_{max}.
Using K_m = 5.7 mg/L

$$\text{Current phenytoin plasma level } 7 = \frac{5.7 \times (350 \times 1 \times 0.92)}{V_{max} - (350 \times 1 \times 0.92)}$$

$$7 = \frac{1834.4}{V_{max} - 322}$$

$$V_{max} - 322 = \frac{1834.4}{7}$$

$$V_{max} = 262.2 + 322$$

$$V_{max} = 584 \text{ mg/day}$$

4. Calculate the dose required to obtain a plasma level of 10 mg/L at steady state:

$$\frac{S \times F \times \text{dose}}{T} = \frac{V_{max} \times C^{ss}}{K_m + C^{ss}}$$

$$\frac{S \times F \times \text{dose}}{1} = \frac{584 \times 10}{5.7 + 10}$$

$$\text{Dose} = \frac{371.97}{0.92}$$

$$\text{Dose} = 404 \text{ mg/day}$$

The nearest practical dose would be 400 mg per day and a level checked again in 2 weeks.

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4 Drug interactions

H. K. R. Thanacoody

Key points

- Drug interactions can cause significant patient harm and are an important cause of morbidity.
- Most clinically important drug interactions occur as a result of either decreased drug activity with diminished efficacy or increased drug activity with exaggerated or unusual effects. Drugs with a narrow therapeutic range, such as theophylline, lithium and digoxin, or a steep dose–response curve, such as anticoagulants, oral contraceptives and anti-epileptics, are often implicated.
- The most important pharmacokinetic interactions involve drugs that can induce or inhibit enzymes in the hepatic cytochrome P450 system.
- Pharmacodynamic interactions are difficult to classify but their effects can often be predicted when the pharmacology of co-administered drugs is known.
- In many cases, potentially interacting drugs can be given concurrently provided the possibility of interaction is kept in mind and any necessary changes to dose or therapy are initiated promptly. In some situations, however, concurrent use of potentially interacting drugs should be avoided altogether.
- Suspected adverse drug interactions should be reported to the appropriate regulatory authority as for other adverse drug reactions.

Drug interactions have been recognised for over 100 years. Today, with the increasing availability of complex therapeutic agents and widespread polypharmacy, the potential for drug interactions is enormous and they have become an increasingly important cause of adverse drug reactions (ADR).

Despite regulatory requirements to define the safety profile of new medicines including their potential for drug–drug interactions before marketing, the potential for adverse interactions is not always evident. This was illustrated by the worldwide withdrawal of the calcium channel blocker mibefradil, within months of launch, following reports of serious drug interactions (Li Wan Po and Zhang, 1998). In the past decade, a number of medicines have been either withdrawn from the market, for example, terfenadine, grepafloxacin and cisapride, or had their use restricted because of prolongation of the QT interval on the electrocardiogram, for example, thioridazine. Drug interactions are an important cause of QT prolongation which increases the risk of developing a life-threatening ventricular arrhythmia known as torsade de pointes (Roden, 2004).

The increasing availability and non-prescription use of herbal and complementary medicines has also led to greater awareness of their potential for adverse interactions. St John's wort, a herbal extract used for treatment of depression, can cause serious interactions as a result of its enzyme-inducing effects. Drug interactions with food and drink are also known to occur, exemplified by the well-known interaction between monoamine oxidase inhibitor antidepressants (MAOIs) and tyramine-containing foodstuffs. Grapefruit juice is a potent inhibitor of cytochrome P450 3A4 and causes clinically relevant interactions with a number of drugs including simvastatin and atorvastatin, thereby increasing the risk of statin-induced adverse reactions such as myopathy and myositis.

Although medical literature is awash with drug interaction studies and case reports of adverse drug interactions, only a relatively small number of these are likely to cause clinically significant consequences for patients. The recognition of clinically significant interactions requires knowledge of the pharmacological mechanisms of drug interactions and a thorough understanding of high-risk drugs and vulnerable patient groups.

Definition

An interaction is said to occur when the effects of one drug are altered by the co-administration of another drug, herbal medicine, food, drink or other environmental chemical agents (Baxter, 2010). The net effect of the combination may manifest as an additive or enhanced effect of one or more drugs, antagonism of the effect of one or more drugs, or any other alteration in the effect of one or more drugs.

Clinically significant interactions refer to a combination of therapeutic agents which have direct consequences on the patient's condition. Therapeutic benefit can be obtained from certain drug interactions, for example, a combination of different antihypertensive drugs may be used to improve blood pressure control or an opioid antagonist may be use to reverse the effect of an overdose of morphine. In this chapter, we will concentrate on clinically significant interactions which have the potential for undesirable effects on patient care.

Epidemiology

Accurate estimates of the incidence of drug interactions are difficult to obtain as published studies frequently use different criteria for defining a drug interaction, and for distinguishing between clinically significant and non-significant interactions. Some of the early studies uncritically compared prescribed drugs with lists of possible drug interactions without taking into account their potential clinical significance.

The reported incidence of drug–drug interactions in hospital admissions ranged from 0% to 2.8% in a review which included nine studies, all of which had some design flaws (Jankel and Fitterman, 1993). In the Harvard Medical Practice Study of adverse events, 20% of events in acute hospital inpatients were drug related. Of these, 8% were considered to be due to a drug interaction, suggesting that interactions are responsible for less than 2% of adverse events in this patient group (Leape et al., 1992).

In a 1-year prospective study of patients attending an Emergency Department, 3.8% resulted from a drug–drug interaction and most of these led to hospital admissions (Raschett et al., 1999). In a prospective UK study carried out on hospital inpatients, ADR were responsible for hospital admission in 6.5% of cases. Drug interactions were involved in 16.6% of adverse reactions, therefore being directly responsible for leading to hospital admission in approximately 1% of cases (Pirmohamed et al., 2004).

Few studies have attempted to quantify the incidence of drug–drug interactions in the outpatient hospital setting and in the community. In the early 1990s, a community pharmacy study in the USA revealed a 4.1% incidence of interactions, while a Swedish study reported an incidence of 1.9%. In the outpatient setting, the availability of newer drugs for a variety of chronic conditions has increased the risk of drug–drug interactions in this patient group.

Although the overall incidence of serious adverse drug interactions is low, it remains a potentially preventable cause of morbidity and mortality.

Susceptible patients

The risk of drug interactions increases with the number of drugs used. In a hospital study, the rate of ADR in patients taking 6–10 drugs was 7%, rising to 40% in those taking 16–20 drugs, with the exponential rise being largely attributable to drug interactions (Smith et al., 1969). In a high-risk group of emergency department patients, the risk of potential adverse drug interaction was 13% in patients taking 2 drugs and 82% in those taking 7 or more drugs (Goldberg et al., 1996).

Although polypharmacy is common and often unavoidable, it places certain patient groups at increased risk of drug interactions. Patients at particular risk include those with hepatic or renal disease, those on long-term therapy for chronic disease, for example, HIV infection, epilepsy, diabetes, patients in intensive care, transplant recipients, patients undergoing complicated surgical procedures and those with more than one prescriber. Critically ill and elderly patients are at increased risk not only because they take more medicines but also because of impaired homeostatic mechanisms that might otherwise counteract some of the unwanted effects. Interactions may occur in some individuals but not in others. The effects of interactions involving drug metabolism may vary greatly in individual patients because of differences in the rates of drug metabolism and in susceptibility to microsomal enzyme induction. Certain drugs are frequently implicated in drug interactions and require careful attention (Box 4.1).

Box 4.1 Examples of drugs with high risk of interaction

Concentration-dependent toxicity
Digoxin
Lithium
Aminoglycosides
Cytotoxic agents
Warfarin

Steep dose–response curve
Verapamil
Sulphonylureas
Levodopa

Patient dependent on therapeutic effect
Immunosuppressives, e.g., ciclosporin, tacrolimus
Glucocorticoids
Oral contraceptives
Antiepileptics
Antiarrhythmics
Antipsychotics
Antiretrovirals

Saturable hepatic metabolism
Phenytoin
Theophylline

Mechanisms of drug interactions

Drug interactions are conventionally discussed according to the mechanisms involved. These mechanisms can be conveniently divided into those with a pharmacokinetic basis and those with a pharmacodynamic basis. Drug interactions often involve more than one mechanism. There are some situations where drugs interact by unique mechanisms, but the most common mechanisms are discussed in this section.

Pharmacokinetic interactions

Pharmacokinetic interactions are those that affect the processes by which drugs are absorbed, distributed, metabolised or excreted. Due to marked interindividual variability in these processes, these interactions may be expected but their extent cannot be easily predicted. Such interactions may result in a change in the drug concentration at the site of action with subsequent toxicity or decreased efficacy.

Absorption

Following oral administration, drugs are absorbed through the mucous membranes of the gastro-intestinal tract. A number of factors can affect the rate of absorption or the extent of absorption (i.e. the total amount of drug absorbed).

Changes in gastro-intestinal pH. The absorption of a drug across mucous membranes depends on the extent to which it exists in the non-ionised, lipid-soluble form. The ionisation state depends on the pH of its milieu, the pK_a of the drug and formulation factors. Weakly acidic drugs, such as the salicylates, are better absorbed at low pH because the non-ionised form predominates.

An alteration in gastric pH due to antacids, histamine H_2 antagonists or proton pump inhibitors therefore has the potential to affect the absorption of other drugs. The clinical significance of antacid-induced changes in gastric pH is not certain, particularly since relatively little drug absorption occurs in the stomach. Changes in gastric pH tend to affect the rate of absorption rather than the extent of absorption, provided that the drug is acid labile. Although antacids could theoretically be expected to markedly influence the absorption of other drugs via this mechanism, in practice, there are very few clinically significant examples. Antacids, histamine H_2 antagonists and omeprazole can significantly decrease the bioavailability of ketoconazole and itraconazole, which require gastric acidity for optimal absorption, but the absorption of fluconazole and voriconazole is not significantly altered by changes in gastric pH.

The alkalinising effects of antacids on the gastro-intestinal tract are transient and the potential for interaction may be minimised by leaving an interval of 2–3 h between the antacid and the potentially interacting drug.

Adsorption, chelation and other complexing mechanisms. Certain drugs react directly within the gastro-intestinal tract to form chelates and complexes which are not absorbed. The drugs most commonly implicated in this type of interaction include tetracyclines and the quinolone antibiotics that can complex with iron, and antacids containing calcium, magnesium and aluminium. Tetracyclines can chelate with divalent or trivalent metal cations such as calcium, aluminium, bismuth and iron to form insoluble complexes, resulting in greatly reduced plasma tetracycline concentrations.

Bisphosphonates are often co-prescribed with calcium supplements in the treatment of osteoporosis. If these are taken concomitantly, however, the bioavailability of both is significantly reduced, with the possibility of therapeutic failure.

The absorption of some drugs may be reduced if they are given with adsorbents such as charcoal or kaolin, or anionic exchange resins such as colestyramine or colestipol. The absorption of propranolol, digoxin, warfarin, tricyclic antidepressants, ciclosporin and levothyroxine is reduced by colestyramine.

Most chelation and adsorption interactions can be avoided if an interval of 2–3 h is allowed between doses of the interacting drugs.

Effects on gastro-intestinal motility. Since most drugs are largely absorbed in the upper part of the small intestine, drugs that alter the rate at which the stomach empties its contents can affect absorption. Drugs with anticholinergic effects, such as tricyclic antidepressants, phenothiazines and some antihistamines, decrease gut motility and delay gastric emptying. The outcome of the reduced gut motility can either be an increase or a decrease in drugs given concomitantly. For example, tricyclic antidepressants can increase dicoumarol absorption, probably as a result of increasing the time available for its dissolution and absorption. Anticholinergic agents used in the management of movement disorders have been shown to reduce the bioavailability of levodopa by as much as 50%, possibly as a result of increased metabolism in the intestinal mucosa.

Opioids such as diamorphine and pethidine strongly inhibit gastric emptying and greatly reduce the absorption rate of paracetamol, without affecting the extent of absorption. Codeine, however, has no significant effect on paracetamol absorption. Metoclopramide increases gastric emptying and increases the absorption rate of paracetamol, an effect which is used to therapeutic advantage in the treatment of migraine to ensure rapid analgesic effect. It also accelerates the absorption of propranolol, mefloquine, lithium and ciclosporin. This type of interaction is rarely clinically significant.

Induction or inhibition of drug transport proteins. The oral bioavailability of some drugs is limited by the action of drug transporter proteins, which eject drugs that have diffused across the gut lining back into the gut. At present, the most well-characterised drug transporter is P-glycoprotein. Digoxin is a substrate of P-glycoprotein and drugs that inhibit P-glycoprotein, such as verapamil, may increase digoxin bioavailability with the potential for digoxin toxicity (DuBuske, 2005).

Malabsorption. Drugs such as neomycin may cause a malabsorption syndrome leading to reduced absorption of drugs such as digoxin. Orlistat is a specific long-acting inhibitor of gastric and pancreatic lipases, thereby preventing the hydrolysis of dietary fat to free fatty acids and triglycerides. This can theoretically lead to reduced absorption of fat-soluble drugs co-administered with orlistat. There has been recent concern about potential decreased absorption of levothyroxine and anti-epileptic drugs such as valproate sodium and lamotrigine, although the exact mechanism for the postulated interactions is presently unclear.

Most of the interactions that occur within the gut result in reduced rather than increased absorption. It is important to recognise that the majority result in changes in absorption rate, although in some instances the total amount (i.e. extent) of drug absorbed is affected. For drugs that are given chronically on a multiple dose regimen, the rate of absorption is usually unimportant provided the total amount of drug absorbed is not markedly altered. On the other hand, delayed absorption can be clinically significant where the drug affected has a short half-life or where it is important to achieve high plasma concentrations rapidly, as may be the case with analgesics or hypnotics. Absorption interactions can often be avoided by allowing an interval of 2–3 h between administration of the interacting drugs.

Drug distribution

Following absorption, a drug undergoes distribution to various tissues including to its site of action. Many drugs and their metabolites are highly bound to plasma proteins. Albumin is the main plasma protein to which acidic drugs such as warfarin are bound, while basic drugs such as tricyclic antidepressants, lidocaine, disopyramide and propranolol are generally bound to α_1-acid glycoprotein. During the process of distribution, drug interactions may occur, principally as a result of displacement from protein-binding sites. A drug displacement interaction is defined as a reduction in the extent of plasma protein binding of one drug caused by the presence of another drug, resulting in an increased free or unbound fraction of the displaced drug. Displacement from plasma proteins can be demonstrated in vitro for many drugs and has been thought to be an important mechanism underlying many interactions in the past. However, clinical pharmacokinetic studies suggest that, for most drugs, once displacement from plasma proteins occurs, the concentration of free drug rises temporarily, but falls rapidly back to its previous steady-state concentration due to metabolism and distribution. The time this takes will depend on the half-life of the displaced drug. The short-term rise in the free drug concentration is generally of little clinical significance but may need to be taken into account in therapeutic drug monitoring. For example, if a patient taking phenytoin is given a drug which displaces phenytoin from its binding sites, the total (i.e. free plus bound) plasma phenytoin concentration will fall even though the free (active) concentration remains the same.

There are few examples of clinically important interactions which are entirely due to protein-binding displacement. It has been postulated that a sustained change in steady-state free plasma concentration could arise with the parenteral administration of some drugs which are extensively bound to plasma proteins and non-restrictively cleared, that is, the efficiency of the eliminating organ is high. Lidocaine has been given as an example of a drug fitting these criteria.

Drug metabolism

Most clinically important interactions involve the effect of one drug on the metabolism of another. Metabolism refers to the process by which drugs and other compounds are biochemically modified to facilitate their degradation and subsequent removal from the body. The liver is the principal site of drug metabolism, although other organs such as the gut, kidneys, lung, skin and placenta are involved. Drug metabolism consists of phase I reactions such as oxidation, hydrolysis and reduction, and phase II reactions, which primarily involve conjugation of the drug with substances such as glucuronic acid and sulphuric acid. Phase I metabolism generally involves the cytochrome P450 (CYP450) mixed function oxidase system. The liver is the major site of cytochrome 450-mediated metabolism, but the enterocytes in the small intestinal epithelium are also potentially important.

CYP450 isoenzymes. The CYP450 system comprises 57 isoenzymes, each derived from the expression of an individual gene. As there are many different isoforms of these enzymes, a classification for nomenclature has been developed, comprising a family number, a subfamily letter and a number for an individual enzyme within the subfamily (Wilkinson, 2005). Four main subfamilies of P450 isoenzymes are thought to be responsible for most (about 90%) of the metabolism of commonly used drugs in humans: CYP1, CYP2, CYP3 and CYP4. The most extensively studied isoenzyme is CYP2D6, also known as debrisoquine hydroxylase. Although there is overlap, each cytochrome 450 isoenzyme tends to metabolise a discrete range of substrates. Of the many isoenzymes, a few (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) appear to be responsible for the human metabolism of most commonly used drugs.

The genes that encode specific cytochrome 450 isoenzymes can vary between individuals and, sometimes, ethnic groups. These variations (polymorphisms) may affect metabolism of substrate drugs. Interindividual variability in CYP2D6 activity is well recognised (see Chapter 5). It shows a polymodal distribution and people may be described according to their ability to metabolise debrisoquine. Poor metabolisers tend to have reduced first-pass metabolism, increased plasma levels and exaggerated pharmacological response to this drug, resulting in postural hypotension. By contrast, ultra-rapid metabolisers may require considerably higher doses for a standard effect. About 5–10% of white Caucasians and up to 2% of Asians and black people are poor metabolisers.

The CYP3A family of P450 enzymes comprises two isoenzymes, CYP3A4 and CYP3A5, so similar that they cannot be easily distinguished. CYP3A is probably the most important of all drug-metabolising enzymes because it is abundant in both the intestinal epithelium and the liver and it has the ability to metabolise a multitude of chemically unrelated drugs from almost every drug class. It is likely that CYP3A is involved in the metabolism of more than half the therapeutic agents that undergo alteration by oxidation. In contrast to other cytochrome 450 enzymes, CYP3A shows continuous unimodal distribution, suggesting that genetic factors play a minor role in its regulation. Nevertheless, the activity of the enzyme can vary markedly among members of a given population.

The effect of a cytochrome 450 isoenzyme on a particular substrate can be altered by interaction with other drugs. Drugs may be themselves substrates for a cytochrome 450 isoenzyme and/or may inhibit or induce the isoenzyme. In most instances, oxidation of a particular drug is brought about by several CYP isoenzymes and results in the production of several metabolites. So, inhibition or induction of a single isoenzyme would have little effect on plasma levels of the drug. However, if a drug is metabolised primarily by a single cytochrome 450 isoenzyme, inhibition or induction of this enzyme would have a major effect on the plasma concentrations of the drug. For example, if erythromycin (an inhibitor of CYP3A4) is taken by a patient being given carbamazepine (which is extensively metabolised by CYP3A4), this may lead to toxicity due to higher concentrations of carbamazepine. Table 4.1 gives examples of some drug substrates, inducers and inhibitors of the major cytochrome 450 isoenzymes.

Table 4.1 Examples of drug substrates, inducers and inhibitors of the major cytochrome P450 enzymes

P450 isoform	Substrate	Inducer	Inhibitor
CYP1A2	Caffeine Clozapine Imipramine Olanzapine Theophylline Tricyclic antidepressants R-warfarin	Omeprazole Lansoprazole Phenytoin Tobacco smoke	Amiodarone Cimetidine Fluoroquinolones Fluvoxamine
CYP2C9	Diazepam Diclofenac Losartan Statins SSRIs S-warfarin	Barbiturates Rifampicin	Amiodarone Azole antifungals Isoniazid
CYP2C19	Cilostazol Diazepam Lansoprazole	Carbamazepine Rifampicin Omeprazole	Cimetidine Fluoxetine Tranylcypromine
CYP2D6	Amitriptyline Codeine Dihydrocodeine Flecainide Fluoxetine Haloperidol Imipramine Nortriptyline Olanzapine Ondansetron Opioids Paroxetine Propranolol Risperidone Thioridazine Tramadol Venlafaxine	Dexamethasone Rifampicin	Amiodarone Bupropion Celecoxib Duloxetine Fluoxetine Paroxetine Ritonavir Sertraline
CYP2E1	Enflurane Halothane	Alcohol (chronic) Isoniazid	Disulfiram
CYP3A4	Amiodarone Terfenadine Ciclosporin Corticosteroids Oral contraceptives Tacrolimus R-warfarin Calcium channel blockers Donepezil Benzodiazepines Cilostazol	Carbamazepine Phenytoin Barbiturates Dexamethasone Primidone Rifampicin St John's wort Bosentan Efavirenz Nevirapine	Cimetidine Clarithromycin Erythromycin Itraconazole Ketoconazole Grapefruit juice Aprepitant Diltiazem Protease inhibitors Imatinib Verapamil

Enzyme induction. The most powerful enzyme inducers in clinical use are the antibiotic rifampicin and antiepileptic agents such as barbiturates, phenytoin and carbamazepine. Some enzyme inducers, notably barbiturates and carbamazepine, can induce their own metabolism (autoinduction). Cigarette smoking, chronic alcohol use and the herbal preparation St John's wort can also induce drug-metabolising enzymes. Since the process of enzyme induction requires new protein synthesis, the effect usually develops over several days or weeks after starting an enzyme-inducing agent. Similarly, the effect generally persists for a similar period following drug withdrawal. Enzyme-inducing drugs with short half-lives such as rifampicin will induce metabolism more rapidly than inducers with longer half-lives, for example, phenytoin, because they reach steady-state concentrations more rapidly. There is evidence that the enzyme induction process is dose dependent, although some drugs may induce enzymes at any dose.

Enzyme induction usually results in a decreased pharmacological effect of the affected drug. St John's wort is now known to be a potent inducer of CYP3A (Mannel, 2004). Thus, when a patient receiving ciclosporin, tacrolimus, HIV-protease inhibitors, irinotecan or imatinib takes St John's wort, there is a risk of therapeutic failure with the affected drug. However, if the affected drug has active metabolites, this may lead to an increased pharmacological effect. The effects of enzyme induction vary considerably between patients and are dependent upon age, genetic factors, concurrent drug treatment and disease state. Some examples of interactions due to enzyme induction are shown in Table 4.2.

Enzyme inhibition. Enzyme inhibition is responsible for many clinically significant interactions. Many drugs act as inhibitors of cytochrome 450 enzymes (see Box 4.2). A strong inhibitor is one that can cause ≥5-fold increase in the plasma area-under-the-curve (AUC) value or more than 80% decrease in clearance of CYP3A substrates. A moderate inhibitor is one that can cause ≥2- but <5-fold increase in the AUC value or

Table 4.2 Examples of interactions due to enzyme induction

Drug affected	Inducing agent	Clinical outcome
Oral contraceptives	Rifampicin Rifabutin Modafinil	Therapeutic failure of contraceptives Additional contraceptive precautions required Increased oestrogen dose required
Ciclosporin	Phenytoin Carbamazepine St John's wort	Decreased ciclosporin levels with possibility of transplant rejection
Paracetamol	Alcohol (chronic)	In overdose, hepatotoxicity may occur at lower doses
Corticosteroids	Phenytoin Rifampicin	Increased metabolism with possibility of therapeutic failure

Box 4.2 Examples of enzyme inhibitors frequently implicated in interactions

Antibacterials
Ciprofloxacin
Clarithromycin
Erythromycin
Isoniazid
Metronidazole

Antidepressants
Duloxetine
Fluoxetine
Fluvoxamine
Nefazodone
Paroxetine
Sertraline

Antifungals
Fluconazole
Itraconazole
Ketoconazole
Miconazole
Voriconazole

Antivirals
Amprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Cardiovascular drugs
Amiodarone
Diltiazem
Quinidine
Verapamil

Gastro-intestinal drugs
Cimetidine
Esomeprazole
Omeprazole

Antirheumatic drugs
Allopurinol
Azapropazone
Phenylbutazone

Other
Aprepitant
Bupropion
Disulfiram
Grapefruit juice
Imatinib
Propoxyphene
Sodium valproate

50–80% decrease in clearance of sensitive CYP3A substrates when the inhibitor is given at the highest approved dose and the shortest dosing interval. A weak inhibitor is one that can cause ≥1.25- but <2-fold increase in the AUC values or 20–50% decrease in clearance of sensitive CYP3A substrates when the inhibitor is given at the highest approved dose and the shortest dosing interval.

Concurrent administration of an enzyme inhibitor leads to reduced metabolism of the drug and hence an increase in the steady-state drug concentration. Enzyme inhibition appears to be dose related. Inhibition of hepatic metabolism of the affected drug occurs when sufficient concentrations of the inhibitor are achieved in the liver, and the effects are usually maximal when the new steady-state plasma concentration is achieved. Thus, for drugs with a short half-life, the effects may be seen within a few days of administration of the inhibitor. Maximal effects may be delayed for drugs with a long half-life.

The clinical significance of this type of interaction depends on various factors, including dosage (of both drugs), alterations in pharmacokinetic properties of the affected drug such as half-life and patient characteristics such as disease state. Interactions of this type are again most likely to affect drugs with a narrow therapeutic range such as theophylline, ciclosporin, oral anticoagulants and phenytoin. For example, starting treatment with an enzyme inhibitor such as ritonavir in a patient taking sildenafil could result in a marked increase in sildenafil plasma concentrations. Some examples of interactions due to enzyme inhibition are shown in Table 4.3.

The isoenzyme CYP3A4, in particular, is present in the enterocytes. Thus, after oral administration of a drug, cytochrome 450 enzymes in the intestine and the liver may reduce

Table 4.3 Examples of interactions due to enzyme inhibition

Drug affected	Inhibiting agent	Clinical outcome
Anticoagulants (oral)	Ciprofloxacin Clarithromycin	Anticoagulant effect increased and risk of bleeding
Azathioprine	Allopurinol	Enhancement of effect with increased toxicity
Clopidogrel	Lansoprazole	Reduced anti-platelet effect
Carbamazepine Phenytoin Sodium valproate	Cimetidine	Antiepileptic levels increased with risk of toxicity
Sildenafil	Ritonavir	Enhancement of sildenafil effect with risk of hypotension

the portion of a dose that reaches the systemic circulation, that is, the bioavailability of the drug. Drug interactions resulting in inhibition or induction of enzymes in the intestinal epithelium can have significant consequences. For example, by selectively inhibiting CYP3A4 in the enterocyte, grapefruit juice can markedly increase the bioavailability of some oral calcium channel blockers, including felodipine (Wilkinson, 2005). Such an interaction is usually considered to be a drug metabolism interaction, even though the mechanism involves an alteration in drug absorption. A single glass of grapefruit juice can cause CYP3A inhibition for 24–48 h and regular consumption may continuously inhibit enzyme activity. Consumption of grapefruit juice is therefore not recommended in patients receiving drugs that are extensively metabolised by CYP3A such as simvastatin, tacrolimus and vardenafil.

Enzyme inhibition usually results in an increased pharmacological effect of the affected drug, but in cases where the affected drug is a pro-drug which requires enzymatic metabolism to active metabolites, a reduced pharmacological effect may result. For example, clopidogrel is metabolised via CYP2C19 to an active metabolite which is responsible for its anti-platelet effect. Proton pump inhibitors such as lansoprazole are inhibitors of CYP2C19 and may lead to reduced effectiveness of clopidogrel when used in combination

Predicting interactions involving metabolism. Predicting drug interactions is not easy for many reasons. First, individual drugs within a therapeutic class may have different effects on an isoenzyme. For example, the quinolone antibiotics ciprofloxacin and norfloxacin inhibit CYP1A2 and have been reported to increase plasma theophylline levels, whereas moxifloxacin is a much weaker inhibitor and appears not to interact in this way. While atorvastatin and simvastatin are metabolised predominantly by the CYP3A4 enzyme, fluvastatin is metabolised by CYP2C9 and pravastatin is not metabolised by the CYP450 system to any significant extent.

Identification of cytochrome P450 isoenzymes involved in drug metabolism using in vitro techniques are now an important step in the drug development process. However, findings

of in vitro studies are not always replicated in vivo and more detailed drug interaction studies may be required to allow early identification of potential interactions. Nevertheless, some interactions affect only a small proportion of individuals and may not be identified unless large numbers of volunteers or patients are studied.

Suspected drug interactions are often described initially in published case reports and are then subsequently evaluated in formal studies. For example, published case reports indicate that some antibiotics reduce the effect of oral contraceptives, although this interaction has not been demonstrated in formal studies. Another factor complicating the understanding of metabolic drug interactions is the finding that there is a large overlap between the inhibitors/inducers and substrates of the drug transporter protein P-glycoprotein and those of CYP3A4. Therefore, both mechanisms may be involved in many of the drug interactions previously thought to be due to effects on CYP3A4.

Elimination interactions

Most drugs are excreted in either the bile or urine. Blood entering the kidneys is delivered to the glomeruli of the tubules where molecules small enough to pass across the pores of the glomerular membrane are filtered through into the lumen of the tubules. Larger molecules, such as plasma proteins and blood cells, are retained. The blood then flows to other parts of the kidney tubules where drugs and their metabolites are removed, secreted or reabsorbed into the tubular filtrate by active and passive transport systems. Interactions can occur when drugs interfere with kidney tubule fluid pH, active transport systems or blood flow to the kidney, thereby altering the excretion of other drugs.

Changes in urinary pH. As with drug absorption in the gut, passive reabsorption of drugs depends on the extent to which the drug exists in the non-ionised lipid-soluble form. Only the non-ionised form is lipid soluble and able to diffuse back through the tubular cell membrane. Thus, at alkaline pH, weakly acidic drugs (pK_a 3.0–7.5) largely exist as ionised lipid-insoluble molecules which are unable to diffuse into the tubule cells and will therefore be lost in the urine. The renal clearance of these drugs is increased if the urine is made more alkaline. Conversely, the clearance of weak bases (pK_a 7.5–10) is higher in acid urine. Strong acids and bases are virtually completely ionised over the physiological range of urinary pH and their clearance is unaffected by pH changes.

This mechanism of interaction is of very minor clinical significance because most weak acids and bases are inactivated by hepatic metabolism rather than renal excretion. Furthermore, drugs that produce large changes in urine pH are rarely used clinically. Urine alkalinisation or acidification has been used as a means of increasing drug elimination in poisoning with salicylates and amphetamines, respectively.

Changes in active renal tubule excretion. Drugs that use the same active transport system in the kidney tubules can compete with one another for excretion. Such competition between drugs can be used to therapeutic advantage. For example, probenecid may be given to increase the plasma concentration of penicillins by delaying renal excretion. With the increasing understanding of drug transporter proteins in the kidneys, it is now known that probenecid inhibits the renal secretion of many other anionic drugs via organic anion transporters (OATs; Lee and Kim, 2004). Increased methotrexate toxicity, sometimes life-threatening, has been seen in some patients concurrently treated with salicylates and some other non-steroidal anti-inflammatory drugs (NSAIDs). The development of toxicity is more likely in patients treated with high-dose methotrexate and those with impaired renal function. The mechanism of this interaction may be multifactorial but competitive inhibition of methotrexate's renal tubular secretion is likely to be involved. If patients taking methotrexate are given salicylates or NSAIDs concomitantly, the dose of methotrexate should be closely monitored.

Changes in renal blood flow. Blood flow through the kidney is partially controlled by the production of renal vasodilatory prostaglandins. If the synthesis of these prostaglandins is inhibited by drugs such as indometacin, the renal excretion of lithium is reduced with a subsequent rise in plasma levels. The mechanism underlying this interaction is not entirely clear, as plasma lithium levels are unaffected by other potent prostaglandin synthetase inhibitors, for example, aspirin. If an NSAID is prescribed for a patient taking lithium, the plasma levels should be closely monitored.

Biliary excretion and the enterohepatic shunt. A number of drugs are excreted in the bile, either unchanged or conjugated, for example, as the glucuronide, to make them more water soluble. Some of the conjugates are metabolised to the parent compound by the gut flora and are then reabsorbed. This recycling process prolongs the stay of the drug within the body but if the gut flora are diminished by the presence of an antibacterial, the drug is not recycled and is lost more quickly. This mechanism has been postulated as the basis of an interaction between broad-spectrum antibiotics and oral contraceptives. Antibiotics may reduce the enterohepatic circulation of ethinyloestradiol conjugates, leading to reduced circulating oestrogen levels with the potential for therapeutic failure. There is considerable debate about the nature of this interaction as the evidence from pharmacokinetic studies is not convincing. However, due to the potential adverse consequences of pill failure, most authorities recommend a conservative approach, including the use of additional contraceptive precautions to cover the short-term use of broad-spectrum antibiotics.

Drug transporter proteins. Drugs and endogenous substances are now known to cross biological membranes not just by passive diffusion but by carrier-mediated processes, often known as transporters. Significant advances in the identification of various transporters have been made and although their contribution to drug interactions is not yet clear, they are now thought to play a role in many interactions formerly attributed to cytochrome 450 enzymes (DuBuske, 2005).

P-glycoprotein (P-gp) is a large cell membrane protein that is responsible for the transport of many substrates, including drugs. It is a product of the ABCB1 gene (previously known as the multidrug resistance gene, MDR1) and a member of the adenosine triphosphate (ATP)-binding cassette family of transport proteins (ABC transporters). P-glycoprotein is found in high levels in various tissues including the renal

proximal tubule, hepatocytes, intestinal mucosa, the pancreas and the blood–brain barrier. P-glycoprotein acts as an efflux pump, exporting substances into urine, bile and the intestinal lumen. Its activity in the blood–brain barrier limits drug accumulation in the central nervous system (CNS). Examples of some possible inhibitors and inducers of P-glycoprotein are shown in Table 4.4. The pumping actions of P-glycoprotein can be induced or inhibited by some drugs. For example, concomitant administration of digoxin and verapamil, a P-glycoprotein inhibitor, is associated with increased digoxin levels with the potential for digoxin toxicity. There is an overlap between CYP3A4 and P-glycoprotein inhibitors, inducers and substrates. Many drugs that are substrates for CYP3A4 are also substrates for P-glycoprotein. Therefore, both mechanisms may be involved in many of the drug interactions initially thought to be due to changes in CYP3A4. Digoxin is an example of the few drugs that are substrates for P-glycoprotein but not CYP3A4.

Pharmacodynamic interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. Sometimes these interactions involve competition for specific receptor sites but often they are indirect and involve interference with physiological systems. They are much less easy to classify than interactions with a pharmacokinetic basis.

Antagonistic interactions

It is to be expected that a drug with an agonist action at a particular receptor type will interact with antagonists at that receptor. For example, the bronchodilator action of a selective β_2-adrenoreceptor agonist such as salbutamol will be antagonised by β-adrenoreceptor antagonists. There are numerous examples of interactions occurring at receptor sites, many of which are used to therapeutic advantage. Specific antagonists may be used to reverse the effect of another drug at receptor sites; examples include the opioid antagonist naloxone and the benzodiazepine antagonist flumazenil. α-Adrenergic agonists such as metaraminol may be used in the management of priapism induced by α-adrenergic antagonists such as phentolamine. There are many other examples of drug classes that have opposing pharmacological actions, such as anticoagulants and vitamin K and levodopa and dopamine antagonist antipsychotics.

Additive or synergistic interactions

If two drugs with similar pharmacological effects are given together, the effects can be additive (see Table 4.5). Although not strictly drug interactions, the mechanism frequently contributes to ADR. For example, the concurrent use of drugs with CNS-depressant effects such as antidepressants, hypnotics, antiepileptics and antihistamines may lead to excessive drowsiness, yet such combinations are frequently encountered. Combinations of drugs with arrhythmogenic potential such as antiarrhythmics, neuroleptics, tricyclic antidepressants and those producing electrolyte imbalance (e.g. diuretics) may lead to ventricular arrhythmias and should be avoided. Another example which has assumed greater importance of late is the risk of ventricular tachycardia and torsade de pointes associated with the concurrent use of more than one drug with the potential to prolong the QT interval on the electrocardiogram (Roden, 2004).

Serotonin syndrome

Serotonin syndrome (SS) is associated with an excess of serotonin that results from therapeutic drug use, overdose or inadvertent interactions between drugs. Although severe cases are uncommon, it is becoming increasingly well recognised in patients receiving combinations of serotonergic drugs (Boyer and Shannon, 2005). It can occur when two or more drugs affecting serotonin are given at the same time or after one serotonergic drug is stopped and another started. The

Table 4.4 Examples of inhibitors and inducers of P-glycoprotein

Inhibitors	Atorvastatin Ciclosporin Clarithromycin Dipyridamole Erythromycin Itraconazole Ketoconazole Propafenone Quinidine Ritonavir Valspodar Verapamil
Inducers	Rifampicin St John's wort

Table 4.5 Examples of additive or synergistic interactions

Interacting drugs	Pharmacological effect
NSAID, warfarin, clopidogrel	Increased risk of bleeding
ACE inhibitors and K-sparing diuretic	Increased risk of hyperkalaemia
Verapamil and β-adrenergic antagonists	Bradycardia and asystole
Neuromuscular blockers and aminoglycosides	Increased neuromuscular blockade
Alcohol and benzodiazepines	Increased sedation
Pimozide and sotalol	Increased risk of QT interval prolongation
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

syndrome is characterised by symptoms including confusion, disorientation, abnormal movements, exaggerated reflexes, fever, sweating, diarrhoea and hypotension or hypertension. Diagnosis is made when three or more of these symptoms are present and no other cause can be found. Symptoms usually develop within hours of starting the second drug but occasionally they can occur later. Drug-induced SS is generally mild and resolves when the offending drugs are stopped. Severe cases occur infrequently and fatalities have been reported.

SS is best prevented by avoiding the use of combinations of several serotonergic drugs. Special care is needed when changing from a selective serotonin reuptake inhibitor (SSRI) to an MAOI and vice versa. The SSRIs, particularly fluoxetine, have long half-lives and SS may occur if a sufficient washout period is not allowed before switching from one to the other. When patients are being switched between these two groups of drugs, the guidance in manufacturers' Summaries of Product Characteristics should be followed. Many drugs have serotonergic activity as their secondary pharmacology and their potential for causing the SS may not be readily recognised, for example linezolid, an antibacterial with monoamine oxidase inhibitory activity has been implicated in several case reports of SS.

Many recreational drugs such as amfetamines and their derivatives have serotonin agonist activity and the SS may ensue following the use of other serotonergic drugs.

Drug or neurotransmitter uptake interactions

Although seldom prescribed nowadays, the MAOIs have significant potential for interactions with other drugs and foods. MAOIs reduce the breakdown of noradrenaline in the adrenergic nerve ending. Large stores of noradrenaline can then be released into the synaptic cleft in response to either a neuronal discharge or an indirectly acting amine. The action of the directly acting amines adrenaline, isoprenaline and noradrenaline appears to be only moderately increased in patients taking MAOIs. In contrast, the concurrent use of MAOIs and indirectly acting sympathomimetic amines such as amphetamines, tyramine, MDMA (ecstasy), phenylpropanolamine and pseudoephedrine can result in a potentially fatal hypertensive crisis. Some of these compounds are contained in proprietary cough and cold remedies. Tyramine, contained in some foods, for example cheese and red wine, is normally metabolised in the gut wall by monoamine oxidase to inactive metabolites. In patients taking MAOI, however, tyramine will be absorbed intact. If patients taking MAOIs also take these amines, there may be a massive release of noradrenaline from adrenergic nerve endings, causing a sympathetic overactivity syndrome, characterised by hypertension, headache, excitement, hyperpyrexia and cardiac arrhythmias. Fatal intracranial haemorrhage and cardiac arrest may result. The risk of interactions continues for several weeks after the MAOI is stopped as new monoamine oxidase enzyme must be synthesised. Patients taking irreversible MAOIs should not take any indirectly acting sympathomimetic amines. All patients must be strongly warned about the risks of cough and cold remedies, illicit drug use and the necessary dietary restrictions.

Drug–food interactions

It is well established that food can cause clinically important changes in drug absorption through effects on gastro-intestinal absorption or motility, hence the advice that certain drugs should not be taken with food, for example, iron tablets and antibiotics. Two other common examples already outlined include the interaction between tyramine in some foods and MAOIs, and the interaction between grapefruit juice and the calcium channel blocker felodipine. With improved understanding of drug metabolism mechanisms, there is greater recognition of the effects of some foods on drug metabolism. The interaction between grapefruit juice and felodipine was discovered serendipitously when grapefruit juice was chosen to mask the taste of ethanol in a study of the effect of ethanol on felodipine. Grapefruit juice mainly inhibits intestinal CYP3A4, with only minimal effects on hepatic CYP3A4. This is demonstrated by the fact that intravenous preparations of drugs metabolised by CYP3A4 are not much affected whereas oral preparations of the same drugs are. Some drugs that are not metabolised by CYP3A4 show decreased levels with grapefruit juice, such as fexofenadine. The probable reason for this is that grapefruit juice inhibits some drug transporter proteins and possibly affects organic anion-transporting polypeptides, although inhibition of P-glycoprotein has also been suggested. The active constituent of grapefruit juice is uncertain. Grapefruit contains naringin, which degrades during processing to naringenin, a substance known to inhibit CYP3A4. Although this led to the assumption that whole grapefruit will not interact, but that processed grapefruit juice will, some reports have implicated the whole fruit. Other possible active constituents in the whole fruit include bergamottin and dihydroxybergamottin.

Initial reports of an interaction between cranberry juice and warfarin, prompting regulatory advice that the international normalised ratio (INR) should be closely monitored in patients taking this combination, have not been confirmed by subsequent controlled studies.

Cruciferous vegetables, such as brussels sprouts, cabbage and broccoli, contain substances that are inducers of the CYP450 isoenzyme CYP1A2. Chemicals formed by burning (e.g. barbecuing) meats additionally have these properties. These foods do not appear to cause any clinically important drug interactions in their own right, but their consumption may add another variable to drug interaction studies, so complicating interpretation.

Drug–herb interactions

There has been a marked increase in the availability and use of herbal products in the UK over the past decade, which include Chinese herbal medicines and Ayurvedic medicines. Up to 24% of hospital patients report using herbal remedies (Constable et al., 2007). Such products often contain

pharmacologically active ingredients which can give rise to clinically significant interactions when used inadvertently with other conventional drugs.

Extracts of *Glycyrrhizin glabra* (liquorice) used for treating digestive disorders may cause significant interactions in patients using digoxin or diuretics. It may exacerbate hypokalaemia induced by diuretic drugs and precipitate digoxin toxicity. Herbal products such as Chinese ginseng (*Panax ginseng*), Chan Su (containing bufalin) and Danshen may also contain digoxin-like compounds which can interfere with digoxin assays, leading to falsely elevated levels being detected.

A number of herbal products have anti-platelet and anticoagulant properties and may increase the risk of bleeding when used with aspirin or warfarin. Herbal extracts containing coumarin-like constituents include Alfalfa (*Medicago sativa*), Angelica (*Angelica archangelica*), Dong Quai (*Angelica polymorpha*, *A. dahurica*, *A. atropurpurea*), chamomile, horse chestnut and red clover (*Trifolium pratense*) which can potentially lead to interactions with warfarin. Herbal products with anti-platelet properties include Borage (*Borago officinalis*), Bromelain (*Ananas comosus*), capsicum, feverfew, garlic, Ginkgo (*Ginkgo biloba*) and turmeric amongst others.

Other examples of drug–herb interactions include enhancement of hypoglycaemic (for example Asian ginseng) and hypotensive (for example hawthorn) effects, and lowering of seizure threshold (for example evening primrose oil and *Shankapushpi*). The most widely discussed drug–herb interactions are those involving St John's wort (*Hypericum* extract) used for depression but these only represent a minority of the potential interactions. It is therefore imperative that patients are specifically asked about their use of herbal medicines as they may not volunteer this information.

Conclusion

Whilst one should acknowledge the impossibility of memorising all potential drug interactions, health care workers need to be alert to the possibility of drug interactions and take appropriate steps to minimise their occurrence. Drug formularies and the Summary of Product Characteristics provide useful information about interactions. Other resources that may also be of use to prescribers include drug safety updates from regulators such as the Medicines and Health care products Regulatory Agency (available at http://www.mhra.gov.uk/index.htm), interaction alerts in prescribing software and the availability of websites which highlight interactions for specific drug classes, for example, HIV drugs (http://www.hiv-druginteractions.org/).

Possible interventions to avoid or minimise the risk of a drug interaction include:

(1) Switching one of the potential interacting drugs.
(2) Allowing an interval of 2–3 h between administration of the interacting drugs.
(3) Altering the dose of one of the interacting drugs, for example, reducing the dose of the drug which is likely to have an enhanced effect as a result of the interaction. In this case, the dose is generally reduced by one-third or half with subsequent monitoring for toxic effects either clinically or by therapeutic drug monitoring. Conversely, if the drug is likely to have reduced effects as a result of the interaction, the patient should be monitored similarly for therapeutic failure and the dose increased if necessary.
(4) Advising patients to seek guidance about their medication if they plan to stop smoking, or start a herbal remedy, as they may need close monitoring during the transition.

Overall, it is important to anticipate when a potential drug interaction might have clinically significant consequences for the patient. In these situations, advice should be given on how to minimise the risk of harm, for example, by recommending an alternative treatment to avoid the combination of risk, by making a dose adjustment or by monitoring the patient closely.

Case studies

Case 4.1

Mrs C is a 62-year-old woman with a history of hypertension, atrial fibrillation and type 2 diabetes. She is a non-smoker and obese. Her current medication comprises flecainide 100 mg twice a day, aspirin 75 mg daily, simvastatin 40 mg and diltiazem 180 mg daily. Mrs C is suffering from a respiratory tract infection and her primary care doctor has prescribed a 5-day course of clarithromycin.

Questions

1. Are there likely to be any clinically significant drug interactions?
2. What advice do you give?

Answers

1. There is potential for interaction between simvastatin and diltiazem and between simvastatin and clarithromycin. Some statins, particularly simvastatin and atorvastatin, are metabolised by cytochrome P450 (CYP3A4) and co-administration of potent inhibitors of this enzyme may particularly increase plasma levels of these statins and so increase the risk of dose-related side effects, including rhabdomyolysis. Clarithromycin is a potent inhibitor of CYP3A4 and diltiazem is a less potent inhibitor.
2. Current advice is that diltiazem and simvastatin may be given together provided the simvastatin dose does not exceed 40 mg daily, so it is reasonable for this therapy to be continued. However, clarithromycin should not be given together with simvastatin. Myopathy and rhabdomyolysis have been reported in patients taking the combination. Mrs C should be advised not to take her simvastatin while she is taking clarithromycin and to start taking it again after she has completed the course of antibiotic.

Case 4.2

A 19-year-old woman is on long-term treatment with minocycline 100 mg daily for acne. She wishes to start using the combined oral contraceptive and her doctor has prescribed a low-strength pill (containing ethinyloestradiol 20 µcg with norethisterone 1 mg). The doctor contacts the pharmacist for advice on whether the tetracycline will interfere with the efficacy of the oral contraceptive.

Question

Is there a clinically significant interaction in this situation?

Answer

Contraceptive failure has been attributed to doxycycline, lymecycline, oxytetracycline, minocycline and tetracycline in about 40 reported cases, seven of which specified long-term antibacterial use. There is controversy about whether or not a drug interaction occurs but if there is one it appears to be very rare. Controlled trials have not shown any effect of tetracycline or doxycycline on contraceptive steroid levels. The postulated mechanism is suppression of intestinal bacteria resulting in a fall in enterohepatic recirculation of ethinyloestradiol. Overall, there is no evidence that this is clinically important.

In the case of long-term use of tetracyclines for acne, a small number of cases of contraceptive failure have been reported. Nevertheless, the only well-designed, case–control study in dermatological practice indicated that the incidence of contraceptive failure due to this interaction could not be distinguished from the general and recognised failure rate of oral contraceptives. The UK Family Planning Association advises that women on long-term antibiotic therapy need only take extra precautions for the first 3 weeks of oral contraceptive use because, after about 2 weeks, the gut flora becomes resistant to the antibiotic. In addition, there is some evidence that ethinyloestradiol may accentuate the facial pigmentation that can be caused by minocycline.

Case 4.3

A 48-year-old man with a history of epilepsy is admitted to hospital with tremor, ataxia, headache, abnormal thinking and increased partial seizure activity. His prescribed medicines are phenytoin 300 mg daily, clonazepam 6 mg daily and fluoxetine 20 mg daily. It transpires that fluoxetine therapy had been initiated 2 weeks previously. The patient's phenytoin level is found to be 35 mg/L; at the last outpatient clinic visit 4 months ago, it was 18 mg/L.

Question

What is the proposed mechanism of interaction between fluoxetine and phenytoin and how should it be managed?

Answer

Fluoxetine is believed to inhibit the metabolism of phenytoin by the cytochrome P450 isoenzyme CYP2C9, potentially leading to increased plasma phenytoin levels. There are a number of published case reports and anecdotal observations of phenytoin toxicity occurring with the combination, but the available evidence is conflicting. A review by the U.S. Food and Drug Administration suggested that a marked increase in plasma phenytoin levels, with accompanying toxicity, can occur within 1–42 days (mean onset time of 2 weeks) after starting fluoxetine. If fluoxetine is added to treatment with phenytoin, the patient should be closely monitored. Ideally the phenytoin plasma levels should be monitored and there may be a need to reduce the phenytoin dosage.

Case 4.4

A 79-year-old man presented to hospital with a 3-day history of increasing confusion and collapse. He had a history of chronic lumbosacral pain, treated with oxycodone 10 mg twice daily and amitriptyline 75 mg daily. Five days before hospital admission he had been prescribed tramadol 100 mg four times daily for worsening sciatica. On admission the patient had a Glasgow Coma Scale of 11 and he was delirious and hallucinating. There were no focal neurological signs. Over the next 2 days he became increasingly unwell, confused and sweaty with pyrexia and muscular rigidity. Biochemical tests showed a metabolic acidosis (base deficit of 10.7) and an elevated creatine kinase level of 380 IU/L. There was no evidence of infection. At this stage a diagnosis of probable serotonin syndrome was made.

Questions

1. What is serotonin syndrome and what drugs are most commonly associated with it?
2. How is serotonin syndrome managed?

Answers

1. Serotonin syndrome is often described as a clinical triad of mental status changes, autonomic hyperactivity and neuromuscular abnormalities. However, not all these features are consistently present in all patients with the disorder. Symptoms arising from a serotonin excess range from diarrhoea and tremor in mild cases to delirium, neuromuscular rigidity, rhabdomyolysis and hyperthermia in life-threatening cases. Disturbance of electrolytes, transaminases and creatine kinase may occur. Clonus is the most important finding in establishing the diagnosis of the serotonin syndrome. The differential diagnosis includes neuroleptic malignant syndrome, sepsis, hepatic encephalopathy, heat stroke, delirium tremens and anticholinergic reactions. Serotonin syndrome may not be recognised in some cases because of its protean manifestations. A wide range of drugs and drug combinations has been associated with the serotonin syndrome, including MAOIs, tricyclic antidepressants, SSRIs, opioids, linezolid and $5HT_1$-agonists. Tramadol is an atypical opioid analgesic with partial µ antagonism and central reuptake inhibition of serotonin (5HT) and noradrenaline. At high doses it may also induce serotonin release. Tramadol is reported as causing serotonin syndrome alone (in a few case reports) and in combination with SSRIs, venlafaxine and atypical antipsychotics.
2. Management of the serotonin syndrome involves removal of the precipitating drugs and supportive care. Many cases typically resolve within 24 h after serotonergic drugs are stopped but symptoms may persist in patients taking medicines with long half-lives or active metabolites. The $5HT_{2A}$-antagonist cyproheptadine and atypical antipsychotic agents with $5HT_{2A}$-antagonist activity, such as olanzapine, have been used to treat serotonin syndrome, although their efficacy has not been conclusively established.

Case 4.5

A 42-year-old woman is on long-term treatment with azathioprine 100 mg daily and bendroflumethiazide 2.5 mg daily. The latter was discontinued after an episode of gout but she had three further episodes over the following year. Her doctor considers prescribing allopurinol as prophylaxis.

Question

Is this likely to cause a clinically significant interaction?

Answer

Azathioprine is metabolised in the liver to mercaptopurine and then converted to an inactive metabolite by the enzyme xanthine oxidase. Allopurinol is an inhibitor of xanthine oxidase and will lead to the accumulation of mercaptopurine which can cause bone marrow suppression and haematological abnormalities such as neutropenia and thrombocytopenia.

The dose of azathioprine should be reduced by at least 50% and close haematological monitoring is required if allopurinol is used concomitantly.

Case 4.6

A 68-year-old woman is on long-term treatment with lansoprazole for gastro-oesophageal reflux disease and warfarin for atrial fibrillation. She is admitted with haematemesis. On direct questioning, she also revealed that she takes various herbal medicines which contain chamomile, horse chestnut, garlic, feverfew, ginseng and St John's wort.

Question

What drug–herb interactions may have contributed to her presentation to hospital?

Answer

Garlic, feverfew and ginseng all inhibit platelet aggregation by inhibiting the production or release of prostaglandins and thromboxanes. In addition, chamomile and horse chestnut contain coumarin-like constituents which can potentiate the anticoagulant effect of warfarin. St John's wort is a potent enzyme inducer and may induce the metabolism of lansoprazole via CYP2C19, thereby reducing the effectiveness of lansoprazole.

Although the effects of herbs individually may be small, their combined effects may lead to serious complications.

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5 Adverse drug reactions

J. Krska and A. R. Cox

Key points

- An adverse drug reaction is an unintended noxious response occurring after the normal use of a drug, which is suspected to be associated with the drug.
- Adverse drug reactions can be classified as type A, which are most common and related to the drug's pharmacological effect, or type B, which are rare and unpredictable, although other classes of reaction can be identified.
- Few adverse reactions are identified during pre-marketing studies; therefore, pharmacovigilance systems to detect new adverse drug reactions are essential.
- Spontaneous reporting schemes are a common method of pharmacovigilance which depend primarily on health professionals.
- Patients are encouraged to contribute to post-marketing surveillance schemes in some countries.
- Adverse drug reactions are a significant cause of morbidity and mortality, are responsible for approximately 1 in 20 hospital admissions and are a considerable financial burden on health systems.
- Predisposing factors for adverse drug reactions include age, female gender, ethnicity, genetic factors, co-morbidities and concomitant medication.
- Many adverse drug reactions may be preventable through rational prescribing and careful monitoring of drug therapy.
- Health professionals need to be able to identify and assess adverse drug reactions and play a major role in preventing their occurrence.
- Patients want to receive information about adverse drug reactions; therefore, communicating the risks of using medicines is an important skill for health professionals.

Introduction

All medicines with the ability to produce a desired therapeutic effect also have the potential to cause unwanted adverse effects. Health professionals should have an awareness of the burden that adverse drug reactions (ADRs) place on health services and the public, the identification and avoidance of ADRs and their important role in post-marketing surveillance of medicines to ensure their continued safety.

Risks associated with medicinal substances are documented throughout history; for example, William Withering's 1785 account provides a meticulous description of the adverse effects of digitalis. However, it was the thalidomide disaster that captured public attention and brought about major regulatory changes in drug safety. Thalidomide was first marketed by Chemie Grünenthal in 1957 and distributed in the UK by Distillers Ltd, whose chief medical advisor stated, 'If all the details of this are true, then it is a most remarkable drug. In short, it is impossible to give a toxic dose.' In 1958, thalidomide was recommended for use in pregnant and nursing mothers without supporting evidence. An Australian doctor, Jim McBride, and a German doctor, Widukund Lenz, independently associated thalidomide exposure with serious birth defects and thalidomide was withdrawn in December 1961. Thalidomide left behind between 8000 and 12,000 deformed children and an unknown number of deaths *in utero*.

The 1970s saw another unexpected and serious adverse reaction. The cardioselective beta-adrenergic receptor blocker practolol, launched in June 1970, was initially associated with rashes, some of which were severe. A case series of psoriasis-like rashes linked to dry eyes, including irreversible scarring of the cornea, led other doctors to report eye damage, including corneal ulceration and blindness, to regulators. Cases of sclerosing peritonitis, a bowel condition associated with significant mortality, were also reported. Practolol had remained on the market for 4 years; over 100,000 people had been treated and hundreds were seriously affected.

Some adverse effects can be more difficult to differentiate from background events occurring commonly in the population. The COX-II selective non-steroidal anti-inflammatory drugs (NSAIDs), celecoxib (introduced 1998) and rofecoxib (introduced 1999), were marketed on the basis of reduced gastro-intestinal ADRs in comparison to other non-selective NSAIDs. Apparent excesses of cardiovascular events, which were noted during clinical trials and in elderly patient groups, were ascribed to the supposed cardio-protective effects of comparator drugs. However, in September 2004, a randomised controlled trial of rofecoxib in the prevention of colorectal cancer showed the drug to be associated with a significantly increased risk of cardiovascular events. Celecoxib was also associated with a dose-related increased risk of cardiovascular events in clinical trials. Rofecoxib was voluntarily withdrawn from the market. Further research has provided evidence of thrombotic risk with non-selective NSAIDs, in particular diclofenac. This risk appears to extend to all NSAID users, irrespective of baseline cardiovascular risk.

Not all drug safety issues are related to real effects. In 1998, a widely-publicised paper by Andrew Wakefield and co-authors, later retracted, alleged a link between MMR vaccine and autism, and led to a crisis in parental confidence in the vaccine. This had a detrimental effect on vaccination rates, resulting in frequent outbreaks of measles and mumps, despite epidemiological and virological studies showing no link between MMR vaccine and autism. The MMR vaccine controversy illustrates how media reporting of drug safety information can influence patients' views of medicines and can cause significant harm. Poor presentation of drug safety issues in the media often creates anxiety in patients about medicines which they may be using, regardless of their benefits.

Assessing the safety of drugs

When drugs are newly introduced to the market, their safety profile will be provisional. While efficacy and evidence of safety must be demonstrated for regulatory authorities to permit marketing, it is not possible to discover the complete safety profile of a new drug prior to its launch. Pre-marketing clinical trials involve on average 2500 patients, with perhaps a hundred patients using the drug for longer than a year. Therefore, pre-marketing trials do not have the power to detect important reactions that occur at rates of 1 in 10,000, or fewer, drug exposures. Often, only pharmacologically predictable ADRs with short onset times may be identified in clinical trials, nor can pre-marketing trials detect ADRs which are separated in time from drug exposure. Additionally, patients within trials are often carefully selected, without the multiple disease states or complex drug histories of patients in whom the drug will eventually become used. Furthermore, the patient's perspective is also frequently excluded from clinical trial safety assessments, with ADRs being assessed only by the clinicians who run them (Basch, 2010). For these reasons, rare and potentially serious adverse effects often remain undetected until a wider population is exposed to the drug. The vigilance of health professionals is an essential factor in discovering these new risks, together with regulatory authorities who continuously monitor reports of adverse effects throughout the lifetime of a marketed medicinal product.

As a result of this monitoring, the safety profile of established drugs is often well known, although new risks are occasionally identified. However, an important part of the therapeutic management of medical conditions is the minimisation of these well-known risks through rational prescribing and careful monitoring of drug therapy. Current evidence suggests that this could be improved.

Definitions

Having clear definitions of what constitutes an ADR is important. The World Health Organization (WHO) defines an ADR as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function' (WHO, 1972). The use of the phrase 'at doses normally used in man' distinguishes the noxious effects of drugs during normal medical use from toxic effects caused by poisoning. Whether an effect is considered noxious depends on both the drug's beneficial effects and the severity of the disease for which it is being used. There is no need to prove a pharmacological mechanism for any noxious response to be termed an ADR.

The terms ADR and adverse drug effect can be used interchangeably; adverse reaction applies to the patient's point of view, while adverse effect applies to the drug. The terms suspected ADR or reportable ADR are commonly used in the context of reporting ADRs to regulatory authorities, for example, through the UK's Yellow Card Scheme, operated by the Medicines and Healthcare Regulatory Authority (MHRA). Although the term 'side effect' and ADR are often used synonymously, the term 'side effect' is distinct from ADR. A side effect is an unintended effect of a drug related to its pharmacological properties and can include unexpected benefits of treatment.

The WHO definition has been criticised for excluding the potential for contamination of a product, ADRs that include an element of error, and ADRs associated with pharmacologically inactive excipients in a product. The use of the term 'drug' also excluded the use of complementary and alternative treatments, such as herbal products. In an attempt to overcome these points, the following definition of an ADR was proposed, 'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regime, or withdrawal of the product' (Edwards and Aronson, 2000).

It is important also to avoid confusion with the term adverse drug event (ADE). An ADR in a patient is an adverse outcome that is attributed to a suspected action of a drug, whereas an ADE is an adverse outcome that occurs after the use of a drug, but which may or may not be linked to use of the drug. It therefore follows that all ADRs are ADEs, but that not all ADEs will be ADRs. This distinction is important in the assessment of the drug safety literature, since the term ADE can be used when it is not possible to suggest a causal link between a drug treatment and an adverse outcome. The suspicion of a causal relationship between the drug and the adverse effect is central to the definition of an ADR.

Classification of ADRs

Classification systems for ADRs are useful for educational purposes, for those working within a regulatory environment and for clarifying thinking on the avoidance and management of ADRs.

Rawlins–Thompson classification

The Rawlins–Thompson system of classification divides ADRs into two main groups: Type A and Type B (Rawlins, 1981). Type A reactions are the normal, but quantitatively exaggerated, pharmacological effects of a drug. They include

the primary pharmacological effect of the drug, as well as any secondary pharmacological effects of the drug, for example, ADRs caused by the antimuscarinic activity of tricyclic antidepressants. Type A reactions are most common, accounting for 80% of reactions.

Type B reactions are qualitatively abnormal effects, which appear unrelated to the drug's normal pharmacology, such as hepatoxicity from isoniazid. They are more serious in nature, more likely to cause deaths, and are often not discovered until after a drug has been marketed. The Rawlins–Thompson classification has undergone further elaboration over the years (Table 5.1) to take account of ADRs that do not fit within the existing classifications (Edwards and Aronson, 2000).

The DoTS system

The DoTS classification is based on *Do*se relatedness, *T*iming and patient *S*usceptibility (Aronson and Ferner, 2003). In contrast to the Rawlins–Thompson classification, which is defined only by the properties of the drug and the reaction, the DoTS classification provides a useful template to examine the various factors that both describe a reaction and influence an individual patient's susceptibility.

DoTS first considers the dose of the drug, as many adverse effects are clearly related to the dose of the drug used. For example, increasing the dose of a cardiac glycoside will increase the risk of digitalis toxicity. In DoTS, reactions are divided into toxic effects (effects related to the use of drugs outside of their usual therapeutic dosage), collateral effects (effects occurring within the normal therapeutic use of the drug) and hyper-susceptibility reactions (reactions occurring in sub-therapeutic doses in susceptible patients). Collateral effects include reactions not related to the expected pharmacological effect of the drug or off-target reactions of the expected therapeutic effect in other body systems. It is worth noting that approximately 20% of newly marketed drugs have their dosage recommendations reduced after marketing, often due to drug toxicity.

The time course of a drug's presence at the site of action can influence the likelihood of an ADR occurring. For example, rapid infusion of furosemide is associated with transient hearing loss and tinnitus, and a constant low dose of methotrexate is more toxic than equivalent intermittent bolus doses. DoTS categorises ADRs as either time-independent reactions or time-dependent reactions. Time-independent reactions occur at any time within the treatment period, regardless of the length of course. Time-dependent reactions range from rapid and immediate reactions, to those reactions which can be delayed.

The final aspect of the DoTS classification system is susceptibility, which includes factors such as genetic predisposition, age, sex, altered physiology, disease and exogenous factors such as drug interactions (Table 5.2)

Factors affecting susceptibility to ADRs

Awareness of the factors which increase the risk of ADRs is key to reducing the burden on individual patients by informing prescribing decisions. The risk that drugs pose to patients

Table 5.1 Extended Rawlins–Thompson classification of adverse drug reactions

Type of reaction	Features	Examples
Type A: Augmented pharmacological effect	Common Predictable effect Dose-dependent Low morbidity Low mortality	Bradycardia associated with a beta-adrenergic receptor antagonist
Type B: Bizarre effects not related to pharmacological effect	Uncommon Unpredictable Not dose-dependent High morbidity High mortality	Anaphylaxis associated with a penicillin antibiotic
Type C: Dose-related and time-related	Uncommon Related to the cumulative dose	Hypothalamic pituitary–adrenal axis suppression by corticosteroids
Type D: Time-related	Uncommon Usually dose-related Occurs or becomes apparent some time after use of the drug	Carcinogenesis
Type E: Withdrawal	Uncommon Occurs soon after withdrawal of the drug	Opiate withdrawal syndrome
Type F: Unexpected failure of therapy	Common Dose-related Often cause by drug interactions	Failure of oral contraceptive in presence of enzyme inducer

Table 5.2 DoTS system of ADR classification

Dose relatedness	Time relatedness	Susceptibility
Toxic effects: ADRs that occur at doses higher than the usual therapeutic dose *Collateral effects*: ADRs that occur at standard therapeutic doses *Hypersusceptability reactions*: ADRs that occur at sub-therapeutic doses in susceptible patients	*Time-independent reactions*: ADRs that occur at any time during treatment. *Time-dependent reactions*: *Rapid reactions* occur when a drug is administered too rapidly. *Early reactions* occur early in treatment then abate with continuing treatment (tolerance). *Intermediate reactions* occur after some delay, but if reaction does not occur after a certain time, little or no risk exists. *Late reactions* risk of ADR increases with continued-to-repeated exposure, including withdrawal reactions. *Delayed reactions* occur some time after exposure, even if the drug is withdrawn before the ADR occurs.	Raised susceptibility may be present in some individuals, but not others. Alternatively, susceptibility may follow a continuous distribution – increasing susceptibility with impaired renal function. *Factors include*: genetic variation, age, sex, altered physiology, exogenous factors (interactions) and disease.

varies dependent on the population exposed and the individual characteristics of patients. Some reactions may be unseen in some populations, outside of susceptible subjects. Other reactions may follow a continuous distribution in the exposed population. Although many susceptibilities may not be known, a number of general factors which affect susceptibility to ADRs and others which affect the propensity of specific drugs to cause ADRs have been elucidated.

Age

Elderly patients may be more prone to ADRs, with age-related decline in both the metabolism and elimination of drugs from the body. They also have multiple co-morbidities and are, therefore, exposed to more prescribed drugs. Chronological age is, therefore, arguably a marker for altered physiological responses to drugs and for the presence of co-morbidities and associated drug use rather than a risk *per se*. As the population ages, the mitigation of preventable ADRs in the elderly will become increasingly important.

Children differ from adults in their response to drugs. Neonatal differences in body composition, metabolism and other physiological parameters can increase the risk of specific adverse reactions. Higher body water content can increase the volume of distribution for water-soluble drugs, reduced albumin and total protein may result in higher concentrations of highly protein bound drugs, while an immature blood–brain barrier can increase sensitivity to drugs such as morphine. Differences in drug metabolism and elimination and end-organ responses can also increase the risk. Chloramphenicol, digoxin, and ototoxic antibiotics such as streptomycin are examples of drugs that have a higher risk of toxicity in the first weeks of life.

Older children and young adults may also be more susceptible to ADRs, a classic example being the increased risk of extrapyramidal effects associated with metoclopramide. The use of aspirin was restricted in those under the age of 12, after an association with Reye's syndrome was found in epidemiological studies. Additionally, children can be exposed to more adverse effects due to the heightened probability of dosing errors and the relative lack of evidence for both safety and efficacy.

Gender

Women may be more susceptible to ADRs. In addition, there are particular adverse reactions that appear to be more common in women than men. For example, impairment of concentration and psychiatric adverse events associated with the anti-malarial mefloquine are more common in females.

Females are more susceptible to drug-induced torsade de pointes, a ventricular arrhythmia linked to ventricular fibrillation and death. Women are also over-represented in reports of torsades de pointes associated with cardiovascular drugs (such as sotalol) and erythromycin. This increased susceptibility in women is thought to be due to their longer QTc interval compared to men.

Co-morbidities and concomitant medicines use

Reductions in hepatic and renal function substantially increase the risk of ADRs. A recent study examining factors that predicted repeat admissions to hospital with ADRs in older patients showed that co-morbidities such as congestive cardiac failure, diabetes, and peripheral vascular, chronic pulmonary, rheumatological, hepatic, renal, and malignant diseases were strong predictors of readmissions for ADRs, while advancing age was not. Reasons for this could be pharmacokinetic and pharmacodynamic changes associated with pulmonary, cardiovascular, renal and hepatic insufficiency, or drug interactions because of multiple drug therapy (Zhang et al., 2009).

Ethnicity

Ethnicity has also been linked to susceptibility to ADRs, due to inherited traits of metabolism. It is known, for example, that the cytochrome P450 genotype, involved in drug metabolism, has varied distribution among people of differing ethnicity. For example, CYP2C9 alleles associated with poor metabolism can affect warfarin metabolism and increase the risk of toxicity. This occurs more frequently in white individuals compared to black individuals.

Examples of ADRs linked to ethnicity include the increased risk of angioedema with the use of ACE inhibitors in black patients (McDowell et al., 2006), the increased propensity of white and black patients to experience central nervous system ADRs associated with mefloquine compared to patients of Chinese or Japanese origin, and differences in the pharmacokinetics of rosuvastatin in Asian patients which may expose them to an increased risk of myopathy. However, susceptibility based on ethnicity could be associated with genetic or cultural factors and ethnicity can be argued to be a poor marker for a patient's genotype.

Pharmacogenetics

Pharmacogenetics is the study of genetic variations that influence an individual's response to drugs, and examines polymorphisms that code for drug transporters, drug-metabolising enzymes and drug receptors. A greater understanding of the genetic basis of variations that affect an individual's response to drug therapy has promised to lead to a new era of personalised medicine. Arguably, pharmacogenetics has yet to deliver on an appreciable scale, the reduction in ADRs that was predicted. However, there are some important examples of severe ADRs that may be avoided with knowledge of a patient's genetic susceptibility.

As already noted, major genetic variation is found in the cytochrome CYP450 group of isoenzymes. This can result in either inadequate responses to drugs, or increased risk of ADRs. Clinically relevant genetic variation has been seen in CYP2D6, CYP2C9, CYP2C19 and CYP3A5. A large effect on the metabolism of drugs can occur with CYP2C9, which accounts for 20% of total hepatic CYP450 content.

The narrow therapeutic index of warfarin, its high inter-individual variability in dosing and the serious consequences of toxicity have made it a major target of pharmacogenomic research. Studies of genetic polymorphisms influencing the toxicity of warfarin have focused on CYP2C9, which metabolises warfarin and vitamin K epoxide reductase (VKOR), the target of warfarin anticoagulant activity. Genetic variation in the VKORC1 gene, which encodes VKOR, influences warfarin dosing by a threefold greater extent than CYP2C9 variants. In 2007, the U.S. Food and Drug Administration (FDA) changed the labelling requirement for warfarin, advising that a lower initial dose should be considered in people with certain genetic variations. However, concerns remain because genetic variation only accounts for a proportion of the variability in drug response and clinicians may obtain a false sense of reassurance from genetic testing leading to complacency in monitoring of therapy. In addition, there appears to be little evidence of additional benefit (Laurence, 2009), in terms of preventing major bleeding events, compared to careful monitoring of the INR (see chapter 23)

A success story for pharmacogenetics is the story of the nucleoside analogue reverse transcriptase inhibitor (NRTI) abacavir. Hypersensitivity skin reactions to abacavir are a particular problem in the treatment of human immunodeficiency virus (HIV) infection. Approximately 5–8% of patients taking abacavir develop a severe hypersensitivity reaction, including symptoms such as fever, rash, arthralgia, headache, vomiting and other gastro-intestinal and respiratory disturbances. Early reports that only a subset of patients was affected, a suspected familial predisposition, the short onset time (within 6 weeks of starting therapy), and an apparent lower incidence in African patients led to suspicion of a genetic cause. Subsequent research revealed a strong predictive association with the human leukocyte antigen HLA-B*5701 allele in Caucasian and Hispanic patients. The presence of the allele can be used to stratify the predicted risk of hypersensitivity as high risk (>70%) for carriers of HLA-B*5701 and low risk (<1%) for non-carriers of HLA-B*5701. Evidence from the practical use of HLA-B*5701 screening has shown substantial falls in the incidence of hypersensitivity reactions, as well as a more general improved compliance with the medication (Lucas et al., 2007).

Another example of a success story for pharmacogenetics involves the cutaneous ADRs Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Both are serious reactions associated with substantial morbidity and mortality in which up to 40% of patients with TEN may die. SJS and TEN have been associated with numerous drugs, although the incidence of these reactions is extremely rare. Anti-epileptic drugs, such as carbamazepine and phenytoin, are known causes of SJS and TEN. The reactions are more common in South East Asian populations, including those from China, Thailand, Malaysia, Indonesia, the Philippines and Taiwan and, to a lesser extent, India and Japan. The presence of HLA allele, HLA-B*1502, for which genetic testing is available, indicates an increased risk of skin reactions for carbamazepine, phenytoin, oxcarbamazepine and lamotrigine. The FDA has recommended HLA-B*1502 screening before using carbamazepine and phenytoin in South East Asian individuals.

Erythrocyte glucose-6-phophatase dehydrogenase (G6PD) deficiency

G6PD deficiency is present in over 400 million people worldwide. It is a sex-linked inherited enzyme deficiency, leading to susceptibility to haemolytic anaemia. Patients with low levels of G6PD are predisposed to haemolysis with oxidant drugs such as primaquine, sulphonamides and nitrofurantoin. There are many variants of the genotype, leading to varied susceptibilities in individuals.

Porphyrias

The porphyrias are a heterogeneous group of inherited disorders of haem biosynthesis. The disorders are transmitted as autosomal dominants, with the exception of the rare congenital porphyria, which is recessive. The effects of drugs are of most importance in patients with acute porphyrias, in which certain commonly prescribed agents may precipitate life-threatening attacks. Other trigger factors include alcohol and changes in sex hormone balance. In the acute porphyrias, patients develop abdominal and neuropsychiatric disturbances, and they excrete in their urine excessive amounts of the porphyrin precursors 5-aminolaevulinic acid (ALA) and porphobilinogen.

A number of drugs may induce excess porphyrin synthesis. However, it is extremely difficult to predict whether or not a drug may cause problems in patients with porphyria and the only factors shown to be clearly linked with porphyrinogenicity are lipid solubility and membrane fluidisation, that is, the ability to disrupt the phospholipid bilayer of the cell membrane. A number of commonly used drugs induce ALA synthase in the liver, but there is wide variation between porphyric patients in their sensitivity to drugs which may trigger attacks. Thus, whereas a single dose of a drug may be sufficient to trigger an acute attack in one patient, another may require a number of relatively large doses of the same drug to produce any clinically significant effect. Lists of drugs which are known to be unsafe and drugs which are thought to be safe for use in acute porphyria are available in the British National Formulary.

Immunological reactions

The immune system is able to recognise drugs as foreign substances, leading to allergic reactions. Smaller drug molecules (<600 Da) can bind with proteins to trigger an immune response, or larger molecules can trigger an immune response directly. The immune response is not related to the pharmacological action of the drug and prior exposure to the drug is required. Immunological reactions are often distinct recognisable responses.

Allergic reactions range from rashes, serum sickness and angioedema to the life-threatening bronchospasm and hypotension associated with anaphylaxis. Patients with a history of atopic or allergic disorders are at higher risk. Immunological (hypersensitivity) reactions are split into four main types (Table 5.3).

Formulation issues contributing to ADRs

Although ADRs caused by product formulation issues are rare, because of stringent regulatory control, examples have occurred and regulatory authorities remain vigilant for such problems. In 1937, the S.E. Massengill Company in the USA developed a liquid preparation of an early antibiotic sulphanilamide which contained 72% diethylene glycol. Over a 2-week period, 353 patients received the elixir, 30% of whom died, including 34 children. Sadly, episodes of diethylene glycol poisoning have been reported in contemporary times, in countries which include Nigeria, India, Argentina and Haiti. In 2006, cough medicines made using glycerin contaminated with diethylene glycol, sourced from China, were responsible for the suspected deaths of over 300 people in Panama.

Osmosin was a slow-release preparation of indometacin which used a novel osmotic pump to deliver the drug through a laser-drilled hole in an impervious tablet. Osmosin was withdrawn in 1983 after 36 fatal gastro-intestinal haemorrhages, suspected to be caused by the tablet becoming lodged against the mucosa of the gastro-intestinal tract and exposing the mucosa to high localised concentrations of indometacin.

Adverse reactions have also been associated with excipient changes. In Australia and New Zealand, a decision to change

Table 5.3 Classification of immunological (hypersensitivity) reactions

Classification	Mechanism	Symptoms/signs and examples
Type I (immediate)	Drug/IgE complex to mast cells release of histamine and leukotrienes.	Pruritis, urticaria, bronchoconstriction, angioedema, hypotension, shock, for example, penicillin anaphylaxis.
Type II (cytotoxic)	IgG and complement binding to (usually) red blood cell. Cytotoxic T-cells lyse the cell.	Haemolytic anaemia and thrombocytopaenia, for example, associated with cephalosporins, penicillins and rifampicin.
Type III (immune complex)	Drug antigen and IgG or IgM form immune complex, attracting macrophages and complement activation.	Cutaneous vasculitis, serum sickness, for example, associated with chlorpromazine and sulphonamides.
Type IV (delayed type)	Antigen presentation with major histocompatibility complex protein to T-cells and cytokine and inflammatory mediator release.	Usually occur after 7–20 days. Macular rashes and organ failure, including Stevens–Johnson syndrome and toxic epidermal necrolysis, for example, associated with neomycin and sulphonamides.

the formulation of phenytoin to one used in the USA led to previously stable patients developing severe adverse reactions, including coma. In the US formulation calcium sulphate dihydrate was replaced with lactose. Unfortunately, it was subsequently found that the calcium salt slowed absorption of phenytoin, while the lactose in the new formulation increased its absorption.

Although excipients are often referred to as inert substances, serious adverse reactions such as anaphylaxis and angioedema have been reported to these substances. Sweeteners, flavourings, colouring agents/dyes and preservatives have all been associated with adverse reactions (Kumar, 2003).

Epidemiology of ADRs

ADRs are widespread, as shown by both systematic reviews and large-scale studies. A review of 69 studies from many countries in 2002 found that ADRs were responsible for an estimated 2.6% of admissions to hospitals and that between 3.5% and 7.3% of in-patients may suffer an ADR. More recent data, however, shows these to be under-estimates. A prospective study (Pirmohamed et al., 2004) found that 6.5% out of 18,820 admissions to medical units were caused by ADRs, with 2.3% of patients dying as a result. A similar prospective study of 3695 in-patient episodes found that 14.7% of those admitted to medical or surgical wards experienced an ADR during their stay. These were more common in women, older patients and in those admitted to surgical wards (Davies et al., 2009).

In primary care, estimates for the incidence of ADRs are more difficult to obtain. Some studies have relied on patients' reports of ADRs, either to postal questionnaires or telephone surveys. These provide varying estimates in ADR incidence and prevalence, but are hampered by the lack of information about non-responders. Nonetheless, estimates are of the order of 25% in the USA (Ghandi et al., 2003) and 30% in the UK (Jarernsiripornkul et al., 2002). A systematic review in 2007 found an incidence of overall ADEs, including ADRs, of 14.9 per 1000 person-months in primary care settings.

A widely quoted figure is that ADRs are between the fourth and sixth leading cause of death in the USA. This is based on an extrapolation of a meta-analysis of studies carried out in the USA, which showed that the incidence of serious ADRs causing hospital admission or occurring during admissions was 6.7% and resulted in an incidence of fatal ADRs of 0.32% (Lazarou et al., 1998). The study has been criticised for its methodology; however, more recent work from Sweden has identified that ADRs were responsible for 3% of deaths there (Wester et al., 2008), while in England ADRs were shown to occur in 0.4% of all patients admitted to hospital. This latter study showed that mortality was higher in those experiencing an ADR than in those who did not. Furthermore, the median length of stay in patients who experienced an ADR was 20 days compared to 8 days and costs associated with in-patient ADRs were calculated to be £171 million annually for the NHS in England (Davies et al., 2009). Costs to the NHS associated with admissions due to ADRs have been estimated as £466 million annually (Pirmohamed et al., 2004).

Pharmacovigilance and epidemiological methods in ADR detection

As already noted, the inherent weaknesses of pre-marketing studies mean that post-marketing surveillance of medicines is essential to detect previously unnoticed adverse effects of treatment. The science of this process is called pharmacovigilance and has been defined as 'the study of the safety of marketed drugs under the practical conditions of clinical use in large communities'. Pharmacovigilance is concerned with the detection, assessment and prevention of adverse effects or any other possible drug-related problems, with the ultimate goal of achieving rational and safe therapeutic decisions in clinical practice.

Spontaneous reporting

Pharmacovigilance uses multiple methods, but the following will focus on spontaneous reporting systems. Spontaneous reporting systems collect data about suspected ADRs in a central database. Cases are not collected in a systematic manner, but accumulate through reports submitted spontaneously by people who make a connection between a drug and a suspected drug-induced event. In the UK, the spontaneous reporting scheme is the Yellow Card scheme. In some countries reporting is a voluntary activity, in others reporting is a legal requirement. There is no evidence that such a requirement increases reporting rates.

Spontaneous reporting has a number of advantages. It is relatively cheap to administer, can follow a product throughout its life and can also accept reports to over-the-counter medication and herbal treatments. Such schemes are, however, passive surveillance systems, which rely on the ability of health professionals to recognise possible ADRs and to distinguish these from symptoms related to underlying disease. It is important to emphasise that only a suspicion of a causal link between a drug and an adverse event is required, not confirmation of the association. One disadvantage of spontaneous reporting systems is their inability to quantify the risk. Such systems supply a numerator (the number of reports), but estimates of the incidence of reactions cannot be made because the population exposed to the drug cannot be ascertained accurately. Furthermore, only a minority of reactions are reported. Spontaneous reports are, however, an important form of evidence leading to drug withdrawals and are crucial for hypothesis generation.

Signal detection

A signal can be described as a possible causal relationship between an adverse event and a drug, which was previously unknown. One useful analogy for signal detection in a

spontaneous reporting database is to think of a radio signal, which is disguised by the background radio 'noise'. Statistical methods of signal generation can be thought of as methods of tuning in to capture the radio signal from the background noise.

Statistical approaches scan the data accumulated through spontaneous reports for 'drug–adverse event pairs' that are disproportionately present within the database as a whole. Such calculations can be run automatically by modern computer systems, providing the opportunity to scan large databases for potential signals of new ADRs. Only rarely will a signal provide such strong evidence that a restriction on use of the drug or its withdrawal is immediately required.

However, while these mathematical approaches do develop hypotheses and give the illusion of an objective estimate of risk, they are not conclusive in themselves. A signal could be due to causes other than the drug. Confounding factors such as particular groups of patients being 'channelled' into receiving a drug can influence reporting. Similarly, reports may be received and analysed by a varied set of people with differing levels of understanding, competence, training, experience and awareness. There is also a tendency for reporting rates to be higher with newly introduced drugs, while articles in the media, regulatory action and even legal cases can provoke reporting of particular reactions. For that reason, the strength of the signal also depends on the quality of the individual spontaneous reports.

Causality assessment

The assessment of whether a drug is responsible for a suspected ADR is of great importance in both the regulatory environment and within the pharmaceutical industry. Reporters to spontaneous reporting schemes are requested to submit suspected ADRs and such reports contain variable levels of information. For example, since re-challenge with the suspected drug is often ethically unacceptable, very few reports contain such information.

As already noted, while a safety signal can arise from the accumulation of reported cases of the event in a database, causality assessment of individual cases may influence the subsequent decision-making process. However, often causality is difficult to prove in pharmacovigilance and a high degree of suspicion may be all that is necessary for regulatory action.

One of the most common methods of causality assessment in use is unstructured clinical assessment, also known as global introspection. Expert review of clinical information is undertaken and a judgement is made about the likelihood of the reaction being due to drug exposure. The assessment of complex situations, often with missing information, is open to variation between different assessors and studies have shown marked disagreement between experts. The WHO international monitoring centre uses global introspection for case assessment, assigning standardised causality categories to suspected ADRs (Table 5.4).

A number of alternative methods of assessing causality have been developed using standardised decision algorithms in an attempt to increase objectivity and reduce assessor bias.

Table 5.4 WHO causality categories for ADRs

Category	Description
Certain	Pharmacologically definitive, with re-challenge if necessary
Probably/likely	Reasonable temporal relationship, unlikely to be attributed to disease processes or other drugs, with reasonable dechallenge response
Possible	Reasonable temporal relationship, but could be explained by concurrent disease or drugs. No information on withdrawal
Unlikely	Temporal relationship improbable, concurrent disease or drugs provide plausible explanation
Conditional/unclassified	An event which requires more data for assessment
Unassessable/ unclassifiable	An event that cannot be judged because of insufficient/contradictory information which cannot be supplemented or verified

One of those most commonly used to assess causality is the Naranjo algorithm. This uses a questionnaire and points are added or taken away based on the responses to each question, such as '*Did the adverse reaction reappear when the drug was re-administered?*' The total score is then used to place the assessed reaction on the following scale: definite, probable, possible or doubtful. Algorithms may be less open to the effects of confounding variables, such as underlying disease states or concomitant drugs, but variation in assessor judgements still occur.

Yellow Card Scheme

The UK's Yellow Card Scheme was established in 1964 following the thalidomide tragedy. The Scheme is operated by the Medicines and Health care Products Regulatory Authority (MHRA). Health care professionals and coroners can submit reports of suspected ADRs using a Yellow Card (found in the British National Formulary) or using an on-line form (http://www.yellowcard.gov.uk). An association between the medicine and the event does not have to be confirmed. A suspicion is sufficient for a report to be submitted. The MHRA request that all serious suspected ADRs are reported by health care professionals concerning established medicines (drugs and vaccines). For newer drugs and vaccines, all suspected ADRs should be reported, even if minor events. Newer medicines under intensive surveillance are identified with an inverted black triangle symbol in product information and standard prescribing texts. Black triangle status is generally maintained for at least 2 years, but the period varies, depending on how much information is obtained about a product's continued

safety. All suspected ADRs occurring in children should be reported even if the medicine has been used off-label.

Information from Yellow Card reports is entered into a database, suspected reactions are categorised using the internationally accepted Medical Dictionary for Regulatory Affairs (MedDRA) and the resultant signals generated by the combined reports are then assessed for causality. Where there is a valid signal which may be an ADR, further work may be required to assess the association further. This could involve requesting further details from reporters, contacting manufacturers, reviewing the literature or conducting pharmacoepidemiological studies. The MHRA estimates that about 40% of the safety signals investigated by the Agency are generated from spontaneous reports.

When new ADRs are identified and an association confirmed, the MHRA may take action in the form of changes to the Summary of Product Characteristics (SmPC) and/or the patient information leaflet (PIL), restricting usage or withdrawing marketing authorisation for the medicine. Withdrawal of marketing authorisation or change in use requires that prescribers and suppliers be informed immediately, but such information is also usually publicised in the media; hence, patients are often aware of these actions and may present with requests for information and advice.

Unfortunately, spontaneous reporting systems, including the Yellow Card Scheme, suffer from severe under-reporting. A systematic review estimated this to be between 82% and 98% (Hazell and Shakir, 2006). There are a variety of reasons for this, including lack of certainty that the medicine caused the symptom, but it is important to emphasise that such certainty is not required. There is also no requirement to provide the patient name or contact details, only those of the actual reporter; hence, confidentiality, also cited as a reason for under-reporting, is no longer an issue. Furthermore, the MHRA have systems in place to check for duplicate reports covering the same incident, thereby eliminating concern about two people submitting reports about the same event in a given patient.

Direct patient reporting

Patients have been permitted to report directly to MHRA since October 2005, with the number of reports increasing steadily since then. Respondents to a survey of UK patient reporters indicated that the facility to report was important and most had an understanding of the purpose of reporting. Many considered it provided an opportunity to influence the content of PILs so that other patients may be better informed. However, there remains a need to further increase awareness of direct patient reporting among both the public and health professionals.

Despite the limited awareness of direct patient reporting, in the main people find it relatively easy to report suspected ADRs (McLernon et al., 2011). The majority of people who reported a suspected ADR identified it as such through issues relating to timing, as outlined in the causality methods used by pharmacovigilance experts, or by accessing information about the medicine from the PIL (Krska et al., 2011). There are a number of countries world-wide which accept patient reports. It has been suggested that these advantages include faster signal generation, avoiding the filtering effect of interpretation of events by health professionals and not least, maintaining the number of reports at a time when reporting by health professionals may be reducing.

A comparison of the content of patient reports submitted to MHRA in the first 2 years of the scheme indicated they were more likely to describe the impact of the ADR than in reports submitted by health professionals. Comparisons of the ADR reports submitted indicated a wider range of ADRs were reported by patients to more medicines. However, the proportion of reactions judged serious by MHRA was similar between both patients and health professionals. Overall, patient reports make a useful contribution to pharmacovigilance.

Published case reports

The first suspicions of a less common or unpredictable reaction may often be seen in a case report from a practitioner. As seen by the cases of thalidomide and practolol, astute and vigilant clinicians submitting case reports to the medical press has been of importance in drug safety. Case reports have been described as a form of non-systematic voluntary reporting. However, reports are not solicited and their appearance in the medical literature is in the gift of medical editors. Editors may demand a causal link, or a case series, requiring higher standards of investigation than regulatory agencies demand from a spontaneous report. These high standards can prevent case histories from reaching publication and deter many clinicians. Furthermore, the time it takes for a case report about a suspected ADR to be published could be several months, during which time more patients may be exposed to the potential risk.

Cohort studies

Cohort studies are prospective pharmacoepidemiological studies that monitor a large group of patients taking a particular drug over a period of time. Ideally such studies compare the incidence of a particular adverse event in two groups of patients, those taking the drug of interest and, another group, matched for all important characteristics except the use of the drug. These studies can indicate the relative risks associated with the adverse event in people exposed to the drug being studied.

Case–control studies

Case–control studies compare the extent of drug usage in a group of patients who have experienced the adverse event with the extent of usage among a matched control group who are similar in potentially confounding factors, but have not experienced the event. By comparing the prevalence of drug taking between the groups, it may be possible to identify whether significantly more people who experienced the event also took a particular drug. Examples of associations which have been established by case–control studies are Reye's

syndrome and aspirin and the relationship between maternal diethylstilboestrol ingestion and vaginal adenocarcinoma in female offspring. Case–control studies are an effective method of confirming whether or not a drug causes a given reaction once a suspicion has been raised. Being retrospective, they rely on good record-keeping about drug use and are not capable of detecting previously unsuspected adverse reactions.

Roles of health professionals

Ensuring medicines are used safely is fundamental to the role of all health professionals who prescribe, supply, administer, monitor or advise on their use. When selecting a medicine for an individual patient, whether this is to be prescribed or sold, the health professional should take account of all relevant patient factors, which may predispose to an ADR. As outlined above, this includes co-morbidities, concomitant drugs, renal and liver function and genetic predisposition. Importantly, it is invaluable to have information about the patient's ADR history. Studies have repeatedly shown that this is poorly documented, leading to inappropriate re-use of medicines which have previously caused problems. Hence, another important role of all health professionals is the documentation of identified ADRs. The patient may have information about this if documentation is insufficient; therefore, questioning the patient about his/her ability to tolerate specific medicines or extracting a full ADR history should be considered at every opportunity.

Identifying and assessing ADRs in clinical practice

Outside the pharmacovigilance environment of companies and regulatory agencies, the identification of potential ADRs is an essential component of clinical practice. Although assessments in practice may lack the formality of expert or algorithmic assessment, they are likely to take into account similar factors, such as whether the clinical event is commonly drug related, the temporal relationship with drug use, a dose relationship and exclusion of other possible causes. A list of such factors is set out in Box 5.1.

There are many triggers which can lead to the suspicion of an ADR. For example, changes in medicines, dose reduction, prescription of medicines used to treat allergic reactions or those frequently used to counteract the effects of other drugs. Simple questioning of patients could easily be incorporated into many aspects of routine care to increase the chances of detecting potential ADRs.

The process of identifying an ADR then involves making a judgement about whether or not a particular event such as a symptom, condition or abnormal test result could be related to a drug used in the patient experiencing the event. The prior experiences of the patient with other medicines should also be taken into consideration.

Every opportunity should be taken to question patients about their experience, to determine whether they perceive any adverse events which could be due to medicines. While routinely asking simple questions is important, it is of equal value to develop a positive attitude towards the patients' perception of suspected ADRs. There is some evidence that health professionals may dismiss patients who report that they have experienced an ADR, but many patients identify such problems appropriately, using factors such as onset, effect of dose change, effect of de-challenge or even re-challenge, as well as the information sources freely accessible to them (Krska et al., 2011). To ascertain whether a symptom reported by a patient can be reasonably suspected of being an ADR requires careful questioning.

As stated above, the MHRA encourage reporting of all serious suspected ADRs to established drugs and all suspected ADRs to new drugs or vaccines. If not reporting themselves, health professionals should consider encouraging others to report. For example, a community pharmacist may have insufficient information to complete a Yellow Card as fully as possible, so may encourage a general practitioner to report. Alternatively, a hospital pharmacist may report on behalf of a consultant clinician. Encouraging others to report also extends to providing information about reporting and educating others, including patients, to report. Community pharmacies and general medical practices should all have a supply of Yellow Cards for patients, but patients may require advice and support in completing these. Pharmacists in particular, because of their role in dispensing prescriptions, may also be involved in educating and supporting others in preventing ADRs and in developing methods to detect ADRs through prescription monitoring.

Box 5.1 Factors that may raise or suppress suspicion of a drug-induced event (Shakir, 2004)

The *temporal relationship* between the exposure to the drug and the subsequent event
The *clinical and pathological characteristics of the event* – events which are known to be related to drug use, rather than disease processes
The *pharmacological plausibility* – based on the observer's knowledge of pharmacology
Existing information in published drug information sources – whether or not the event has been noted by others
Concomitant medication – which may be considered the cause of an event
Underlying and concurrent illnesses – may alter the event or be considered the cause of the event
De-challenge – disappearance of symptoms after dose reduction or cessation of therapy
Re-challenge – reappearance of symptoms after dose increases or recommencement of therapy
Patient characteristics and previous medical history – past history of the patient may colour the view of the event
The potential for *drug interactions*

Preventing ADRs

The majority of ADRs are thought to be preventable; hence, there is potential to dramatically reduce the costs associated with ADRs and possibly also deaths. Assessing preventability is a difficult area, since it involves judgements and many

different methods have been developed for making these judgements. The approach of Hallas et al. (1990) is widely used, providing definitions of avoidability which range from definite (due to a procedure inconsistent with present-day knowledge or good medical practice) to unevaluable (poor data or conflicting evidence). Recent estimates suggest that between 53% and 72% of hospital admissions due to ADEs are preventable, while a meta-analysis (Beijer and de Blaey, 2002) showed that 88% of ADRs causing hospital admission in the elderly were preventable. However, not all ADRs are absolutely preventable and assessments using hindsight are unlikely to replicate clinical decision making at the point of prescribing. Preventability also varies from those with clear solutions, such as the prescribing of a teratogenic drug to a female of child bearing age, to those where the drug increases the risk of an event that occurs within the population.

ADRs can be prevented by checking previous ADR history, minimising the use of drugs known to carry a high risk of ADRs and tailoring drug selection to individuals based on the factors which predispose them to ADRs. Strategies are still required to minimise the burden of ADRs, but many recent initiatives have the potential to do so. For example, electronic decision support, increasing regular review of medicines, improved sharing of information about patients between health care providers and the increasing availability of guidance on drug selection and appropriate use should all increase rational prescribing, which may have an effect on the incidence of ADRs.

Monitoring therapy

Monitoring the effects of drugs either by direct measurement of serum concentration or by measurement of physiological markers is another potential mechanism to reduce the risk of ADRs. For example, it has been estimated that one in four of preventable drug-related hospital admissions are caused by failure to monitor renal function and electrolytes (Howard et al., 2003).

Clozapine, used for the management of treatment resistant schizophrenia and psychosis, is associated with significant risk of agranulocytosis. Mandatory monitoring of white blood cell counts has effectively eliminated the risk of fatal agranulocytosis.

Ideally, advice on monitoring should be clear, provide an evidence-based frequency of monitoring and acceptable values. However, robust evidence for the optimal monitoring frequency is limited, hampering specific guidance on monitoring. Guidelines vary between various expert bodies and drug information sources. An examination of the adequacy of manufacturers' advice on monitoring for haematological ADRs found that advice was too vague to be useful to prescribers (Ferner et al., 2005).

Currently, monitoring is often neglected, although practitioners may take greater care when treating the elderly and those with more co-morbidities (McDowell., 2010). Warfarin remains one of the top 10 drugs involved in drug-induced admissions, despite a clearly defined monitoring requirement.

Explaining risks to patients

Numerous studies have shown that patients want to receive information about side effects, although one study comparing patients' views to those of health professionals found that the latter viewed providing side effect information as of much less importance than patients did in receiving it. One of the main sources of information about ADRs is the PIL, which must be provided every time a medicine is prescribed or supplied. Ultimately, patients then have to make a decision about whether or not to use the medicine. Therefore, they have a right to receive understandable information about the potential for harm that a medicine may cause, to enable them to make an informed decision. While there may still be debate about whether the provision of information on side effects encourages reduced adherence to taking medicines or spurious reporting of adverse effects, it is clear that this information is useful to patients and its availability will increase. Patients do use the PIL when suspected adverse events are experienced, to assist in ascribing the cause of the problem; therefore, as outlined above, side effect information should be understandable and there is now a requirement to test information leaflets with patients prior to granting a marketing authorisation for a medicine.

Patients increasingly access a wide range of information sources about medicines and ADRs themselves; indeed, they are actively encouraged to do so. Hence, they may question judgements about the selection of individual products they have been prescribed or sold. In this situation, the health professional must be able to interpret the information accessed by the patient to ensure it is unbiased and accurate.

The EU recommends using verbal terms to describe the risk of experiencing an ADR, ranging from '*very common*' (for rates of more than 1 in 10) to '*very rare*' (for rates of less than 1 in 10,000). The MHRA advocates combining words with frequencies, for example, '*Common (affects more than 1 in 100 persons)*'. Studies show that patients tend to over-estimate the risk when these are described using words only and that patients differ in their understanding of what the terms mean. Percentages, particularly those below 1%, are also not understood by everybody. This lack of understanding of the risks of experiencing an ADR can potentially reduce willingness to use the medicine.

Another approach is the use of pictures, such as faces, graphs or charts. One example is the 'Paling palette', which is a grid of 1000 stick figures to convey information on the chances of experiencing a particular outcome. A similar method is a 'Cates plot' which is a grid of 100 faces or 1000 faces for rarer events, coloured differently and either smiling or downcast depending on the outcome. An example of a Cates plot is provided in Fig. 5.1. These types of icon grids are mainly used to convey the potential benefits and risks of a particular action, but can also be used to explain the risks of getting a side effect. Cates plots have been used to good effect by the UK's National Prescribing Centre. However, there are people who do not find these easy to understand (Ancker et al., 2006).

Much work has been undertaken on risk communication. It is important to appreciate that, when communicating information

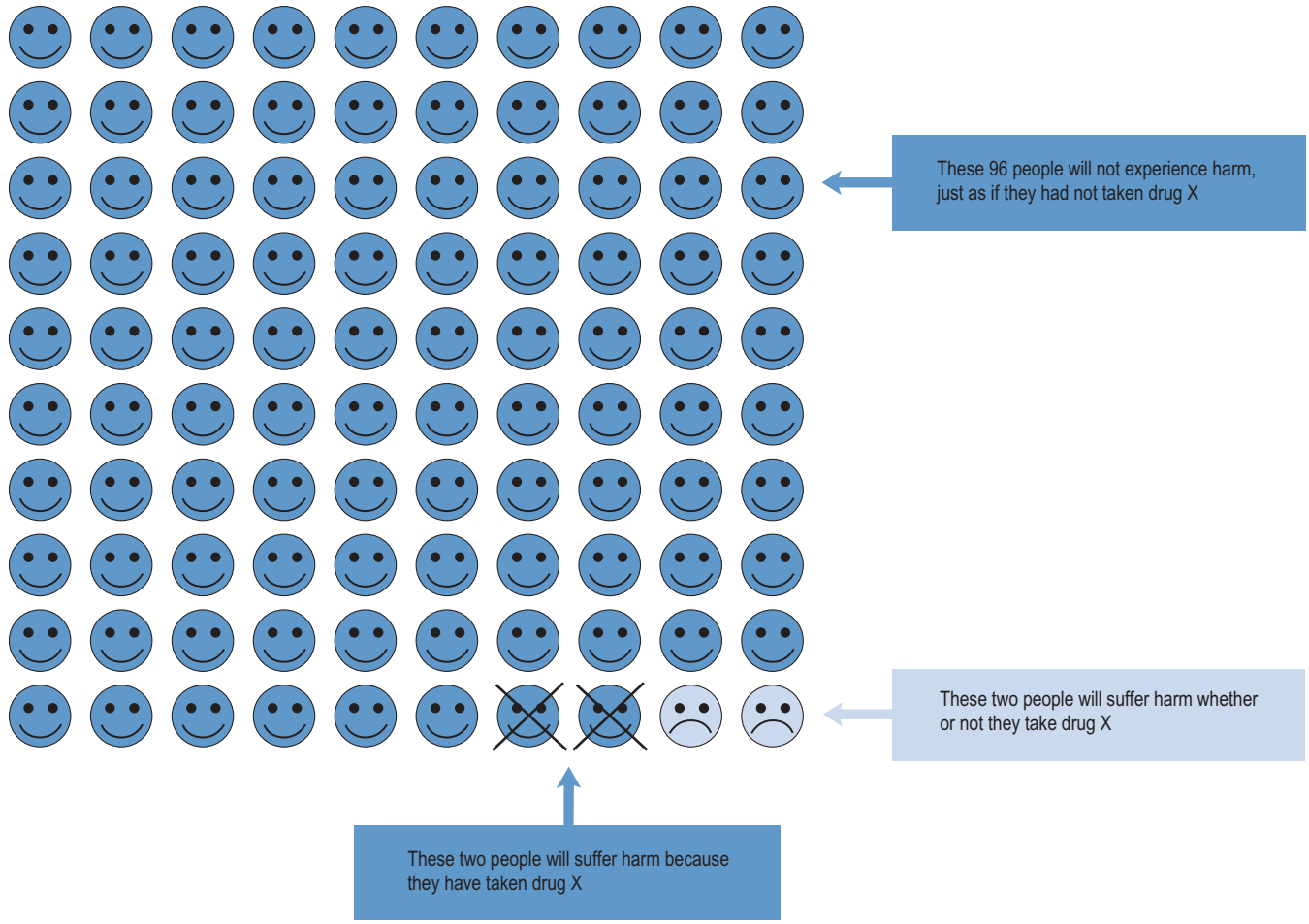

Fig. 5.1 Acute coronary syndrome (ACS) patient decision aid: aspirin plus clopidogrel versus aspirin alone. Copyright National Prescribing Centre, reproduced by permission.

about potential ADRs, how risks are perceived will be affected by the relationship between the health professional and the patient, the patient's prior experience and beliefs, how information is framed and the context in which it is given. Patients may also have views on the acceptability of ADRs, which should be taken into account when selecting a product for an individual. An ADR which is viewed as minor by health professionals may be considered to reduce quality of life by one patient, while another patient may be happy to accept this for the potential benefit the medicine offers. Even when drugs are withdrawn from the market for safety reasons, significant numbers of patients will feel they were willing to accept the harm–benefit of the drug. Communicating the harms and benefits of medicines is, therefore, an important role of health professionals.

Case studies

Case 5.1

Mr KM is a fairly active 69-year-old. He has regularly presented his repeat prescription for atenolol 50 mg daily, aspirin 75 mg daily and simvastatin 40 mg daily to the same community pharmacy for several years. Last month diltiazem SR 60 mg twice daily was added, as he had been getting increasing angina symptoms. He asks for a topical product to treat neck pain, which has developed in the last few days which he puts down to a 'frozen shoulder'.

Questions

1. Could this be an ADR and why did it develop now?
2. Is it appropriate to change to another statin?
3. What actions should the pharmacist take?

Answers

1. Neck pain, 'frozen shoulder' and such descriptions are typical of the muscular pain which is induced by statins. The incidence of mild muscle pain with statins is between 2% and 7% in clinical trials. The onset varies from a few weeks to over 2 years after starting treatment, the incidence is dose-related and the severity ranges from mild aches to severe pain, causing reduced mobility. Older people, who may have reduced renal function or liver function, are at greater risk of statin-induced myopathy.

Diltiazem can inhibit the metabolism of simvastatin due to its actions on cytochrome P450 isoenzyme CYP3A4, thereby increasing the risk of myopathy.

Statin-induced myopathy ranges from mild myopathies and myalgias, to myositis, to rare cases of potentially life-threatening rhabdomyolysis, in which muscle cell walls are disrupted and the

contents leak into the systemic circulation. Muscle pain in patients taking statins should, therefore, always be taken seriously.

2. The problem is associated with all drugs in the class. Although simvastatin and atorvastatin, the most widely prescribed, are both lipophilic and metabolised by cytochrome P450 3A4 and, therefore, may be most likely to cause muscle pain, there is no reliable comparative data on different statins.

3. Creatinine kinase (CK) levels should have been measured before initiating statin therapy, but regardless of whether or not this was done, a CK level should be measured now, plus liver function tests. Mr KM's primary care doctor should be contacted to inform him about the suspected ADR and the patient encouraged to report the ADR via the Yellow Card Scheme. It may be appropriate to discontinue or reduce the dose of the simvastatin, depending on the result of the CK level and the severity of the symptoms. The problem may not resolve immediately on discontinuation. Grapefruit juice can increase blood levels of simvastatin and high alcohol intake increases the risk of myopathy, so the pharmacist should also warn Mr KL about avoiding these.

Case 5.2

A 39-year-old male taking varenicline for smoking cessation reports that he has been suffering from vivid dreams and has become increasingly aggressive towards his family. Last night he had a major argument with his wife. His wife mentioned he hadn't been the same since he started the varenicline and he would like to know if this was a possible cause.

Questions

1. Is varenicline a possible cause of his vivid dreams and aggression?
2. Is this a reportable adverse drug reaction?

Answers

1. Varenicline has been associated with neuropsychiatric ADRs, including depression, suicidal thoughts, suicidal behaviour and aggression. Vivid dreams and other sleep disorders have also been reported. Prescribers have been warned that such reactions have been reported. Assessing the cause of this reaction is difficult, since smoking cessation itself is associated with exacerbations of underlying psychiatric illness and the risk of symptoms of depression. As varenicline dosing starts 1–2 weeks before stopping smoking, a key question is how long the patient has been taking the drug, and if the symptoms appeared before the smoking cessation date.

2. If a health professional considers that a patient's symptoms are a possible ADR to a newer drug, then they should be reported to regulatory authorities (in the UK, this would be through the MHRA's Yellow Card Scheme). Only a suspicion is necessary to report a reaction, not proven causality. In the case of intensively monitored medicines (identified by an inverted black triangle in the BNF), any reaction, no matter how trivial should be reported. Patients can also report directly to regulatory authorities in some countries, including the UK. Neuropsychiatric reactions such as this are commonly reported by patients.

Case 5.3

A 65-year-old man with heart failure is admitted to hospital with a potassium level of 7.1 mmol/L. Already stabilised on lisinopril 20 mg daily, he had recently been started on spironolactone 25 mg daily. He had a serum creatinine of 160 μmol/L.

Questions

1. What is the mechanism of any possible adverse drug reaction?
2. How should future episodes of hyperkalaemia be avoided?

Answers

1. Spironolactone, an aldosterone receptor antagonist, has a beneficial effect on mortality and hospital admission in patients with heart failure. However, spironolactone can increase potassium serum levels due to its effect on aldosterone. When used in combination with ACE inhibitors, serious hyperkalaemia can occur.

Although clinical trials of spironolactone showed no risk, cases have been reported in the literature and other epidemiological studies have indicated that in real-world clinical situations, the incidence of hyperkalaemia is increased.

2. Care should be taken when prescribing spironolactone outside of trial criteria, particularly with regard to renal function. Other susceptibilities for the development of hyperkalaemia include diabetes and the elderly due to reduced aldosterone production. Changes in other therapy should be monitored, as well as episodes of acute illness. Those with mildly increased serum potassium should have a reduced dose of spironolactone. More intensive monitoring of potassium levels at the commencement of therapy might be useful, although the hyperkalaemia can occur months after initiation.

Case 5.4

A 55-year-old woman attending a warfarin out-patient clinic has a raised INR. On questioning it is discovered that she has recently started taking glucosamine for muscle aches for the last 2 weeks.

Questions

1. What is the likelihood that glucosamine was responsible for the rise in the INR?
2. Should this reaction be reported to regulatory authorities?

Answers

1. Glucosamine is a popular supplement purchased for 'joint health'. It is commonly used by older patients. Spontaneous reports of interactions between warfarin and glucosamine have been submitted to UK, Australian and US regulators. Additional cases have been reported in the literature. While there is no known mechanism and no formal interaction studies, the published cases and spontaneous reports are sufficient evidence to suggest a potential interaction. Given the wide use of glucosamine, the interaction may be rare, although under-reporting is common.

Assessment of this individual case requires further questioning to eliminate other confounding factors such as changes in diet or adherence issues.

2. Interactions with, or adverse reactions to, complementary and alternative remedies can be reported to spontaneous reporting schemes, such as the Yellow Card Scheme. Collation of such reports allows regulators to gather further information on the suspected reaction, and any susceptibilities that may in time provide useful information to other users.

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6 Laboratory data

H. A. Wynne and C. Edwards

Key points

- Biochemical and haematological tests provide useful information for the diagnosis, screening, management, prognosis and monitoring of disease and its response to treatment.
- Reference ranges are important guides which generally represent the test values from 95% of the healthy population (mean ± 2 standard deviations).
- A series of values, rather than a single test value, is often required to ensure clinical relevance and eliminate erroneous values due to patient variation and analytical or sampling errors.
- A wide variety of intracellular enzymes may be released into the blood following damage to tissues such as hepatocytes and skeletal muscle. These can be measured in serum to provide useful diagnostic information.
- Commonly requested biochemical test profiles include the so-called 'Us and Es' (urea and electrolytes), liver function tests, troponins and C-reactive protein.
- Commonly requested haematological test profiles include full blood count, differential white cell count, erythrocyte sedimentation rate (ESR), serum folate and vitamin B_{12} and iron status, and clotting screen.
- Drug therapy can cause abnormal test results.
- Drugs can have an important role in preventing or treating abnormalities.

This chapter will consider the common biochemical and haematological tests that are of clinical and diagnostic importance. For convenience, each individual test will be dealt with under a separate heading and a brief review of the physiology and pathophysiology will be given where appropriate to explain the basis of biochemical and haematological disorders.

It is usual for a reference range to be quoted for each individual test (see Tables 6.1 and 6.4). This range is based on data obtained from a sample of the general population which is assumed to be disease-free. Many test values have a normal distribution and the reference values are taken as the mean ± 2 standard deviations (SD). This includes 95% of the population. The 'normal' range must always be used with caution since it takes little account of an individual's age, sex, weight, height, muscle mass or disease state, many of which variables can influence the value obtained. Although reference ranges are valuable guides, they must not be used as sole indicators of health and disease. A series of values rather than a simple test value may be required in order to ensure clinical relevance and to eliminate erroneous values caused, for example, by spoiled specimens or interference from diagnostic or therapeutic procedures. Furthermore, a disturbance of one parameter often cannot be considered in isolation without looking at the pattern of other tests within the group.

Further specific information on the clinical and therapeutic relevance of each test may be obtained by referral to the relevant chapter in this book.

Biochemical data

The homeostasis of various elements, water and acid–base balance are closely linked, both physiologically and clinically. Standard biochemical screening includes several measurements which provide a picture of fluid and electrolyte balance and renal function. These are commonly referred to colloquially as 'Us and Es' (urea and electrolytes) and the major tests are described below.

Sodium and water balance

Sodium and water metabolism are closely interrelated both physiologically and clinically, and play a major role in determining the osmolality of serum.

Water constitutes approximately 60% of body weight in men and 55% in women (women have a greater proportion of fat tissue which contains little water). Approximately two-thirds of body water is found in the intracellular fluid (ICF) and one-third in the extracellular fluid (ECF). Of the ECF 75% is found within interstitial fluid and 25% within serum (Fig. 6.1). Total body water is regulated by the renal action of antidiuretic hormone (ADH), the renin angiotensin–aldosterone system, noradrenaline/norepinephrine and by thirst which is stimulated by rising plasma osmolality.

In general, water permeates freely between the ICF and ECF. Cell walls function as semipermeable membranes, with water movement from one compartment to the other being controlled by osmotic pressure: water moves into the compartment with the higher osmotic concentration. The osmotic content of the two compartments is generally the same, that is, they are isotonic, which ensures normal cell membrane integrity and cellular processes. However, the kidneys are an exception to the rule.

Table 6.1 Biochemical data: typical normal adult reference values measured in serum

Laboratory test	Reference range
Urea and electrolytes	
Sodium	135–145 mmol/L
Potassium	3.4–5.0 mmol/L
Calcium (total)	2.12–2.60 mmol/L
Calcium (ionised)	1.19–1.37 mmol/L
Phosphate	0.80–1.44 mmol/L
Magnesium	0.7–1.00 mmol/L
Creatinine	75–155 µmol/L
Urea	3.1–7.9 mmol/L
Estimated glomerular filtration rate (eGFR)	≥ 90 ml/min/1.73m^2
Glucose	
Fasting	3.3–6.0 mmol/L
Non-fasting	<11.1 mmol/L
Glycated haemoglobin	Non-diabetic subjects <43 mmol/mol Inadequate control >58 mmol/mol
Liver function tests	
Albumin	34–50 g/L
Bilirubin (total)	<19 µmol/L
Enzymes	
Alanine transaminase	<45 U/L
Aspartate transaminase	<35 U/L
Alkaline phosphatase	35–120 U/L
γ-Glutamyl transpeptidase	<70 U/L
Ammonia	
Men	15–50 µmol/L
Female	10–40 µmol/L
Amylase	<100 U/L
Cardiac markers	
Troponin I	(99th percentile of upper reference limit) 0.04 µcg/L
Other tests	
C-reactive protein (CRP)	0–5 mg/L
Osmolality	282–295 mOsmol/kg
Uric acid	0.15–0.47 mmol/L
Parathyroid hormone (adult with normal calcium)	10–65 ng/L
25-Hydroxyvitamin D	>75 nmol/L (optimal) >50 nmol/L (sufficient) 30–50 nmol/L (insufficient) 12–30 nmol/L (deficient) <12 nmol/L (severely deficient)

The osmolality of the ECF is largely determined by sodium and its associated anions, chloride and bicarbonate. Glucose and urea have a lesser, but nevertheless important, role in determining ECF osmolality. Protein, especially albumin, makes only a small (0.5%) contribution to the osmolality of the ECF but is a major factor in determining water distribution between the two compartments. The contribution of proteins to the osmotic pressure of serum is known as the colloid osmotic pressure or oncotic pressure.

The major contributor to the osmolality of the ICF is potassium.

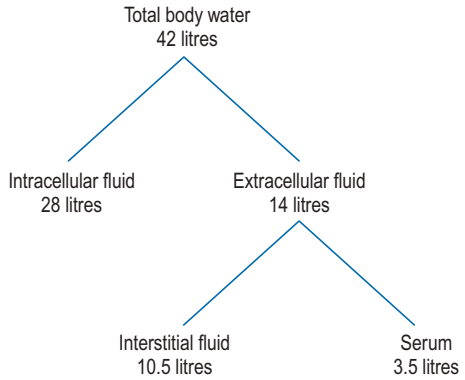

Fig. 6.1 Approximate distribution of water in a 70 kg man.

The amount of water taken in and lost by the body depends on intake, diet, activity and the environment. Over time the intake of water is normally equal to that lost (Table 6.2). The minimum daily intake necessary to maintain this balance is approximately 1100 mL. Of this, 500 mL is required for normal excretion of waste products in urine, whilst the remaining volume is lost via the skin in sweat, via the lungs in expired air, and in faeces. The kidneys regulate water balance, water being filtered, then reabsorbed in variable amounts depending primarily on the level of ADH.

Water depletion

Water depletion will occur if intake is inadequate or loss excessive. Excessive loss of water through the kidney is unusual except in diabetes insipidus or following the overuse of diuretics.

Patients with fever will lose water through the skin and ventilated patients will lose it through the lungs. Diarrhoea causes water depletion. Water loss is usually compensated for if the thirst mechanism is intact or can be responded to, but this may not occur in patients who are unconscious, have swallowing difficulties or are disabled. Severe water depletion may induce cerebral dehydration causing confusion, fits, coma and circulatory failure.

The underlying cause for the water depletion should be identified and treated. Replacement water should be given orally, where possible, or by nasogastric tube, intravenously

Table 6.2 Typical daily water balance for a healthy 70 kg adult

	Input (mL)		Output (mL)
Oral fluids	1400	Urine	1500
Food	700	Lung	400
Metabolic oxidation	400	Skin Faeces	400 200
Total	2500		2500

or subcutaneously as necessary with 5% dextrose in water or, in patients with associated sodium deficits, isotonic saline. Hypotonic saline is sometimes used, but with great caution, where neurologic effects of hypertonicity predominate. Hypernatraemia should be corrected slowly: not more than half of the water deficit should be corrected in the first 12–24 h.

Water excess

Water excess is usually associated with an impairment of water excretion such as that caused by renal failure or the syndrome of inappropriate secretion of the antidiuretic hormone arginine vasopressin (SIADH). This syndrome has several causes including chest infections and some tumours, particularly small cell carcinoma of the lung. Excess intake is rarely a cause of water excess since the healthy adult kidney can excrete water at a rate of up to 2 mL/min. Patients affected usually present with signs consistent with cerebral overhydration, although if it is of gradual onset, over several days, they may be asymptomatic. Hyponatraemia is usually present.

Water and ECF osmolality

If the body water content changes independent of the amount of solute, osmolality will be altered (the normal range is 282–295 mmol/kg of water). A loss of water from the ECF will increase its osmolality and result in the movement of water from the ICF to ECF. This increase in ECF osmolality will stimulate the hypothalamic thirst centres to promote a desire to drink while also stimulating the release of vasopressin or ADH. ADH increases the permeability of the renal collecting ducts to water and promotes water reabsorption with consequent concentration of urine.

If the osmolality of the ECF falls, there is no desire to drink and no secretion of ADH. Consequently, a dilute urine is produced which helps restore ECF osmolality to normal.

The secretion of ADH is also stimulated by angiotensin II, arterial and venous baroreceptors, volume receptors, stress (including pain), exercise and drugs such as morphine, nicotine, tolbutamide, carbamazepine and vincristine. If blood volume decreases by more than 10%, the hypovolaemia stimulates ADH release and overrides control based on osmolality.

Sodium distribution

The body of an average 70 kg man contains approximately 3000 mmol of sodium. Most of this sodium is freely exchangeable and is extracellular. The normal serum range is 135–145 mmol/L. In contrast, the ICF concentration of sodium is only about 10 mmol/L.

Each day approximately 1000 mmol of sodium is secreted into the gut and 25,000 mmol filtered by the kidney. The bulk of this is recovered by reabsorption from the gut and renal tubules. It should be clear, therefore, that partial failure of homeostatic control can potentially have major consequences.

Sodium and ECF volume

The ECF volume is dependent upon total body sodium since sodium is almost entirely restricted to the ECF, and water intake and loss are regulated to maintain a constant concentration of sodium in the ECF compartment.

Sodium balance is maintained by renal excretion. Normally, 70% of filtered sodium is actively reabsorbed in the proximal tubule, with further reabsorption in the loop of Henle. Less than 5% of the filtered sodium load reaches the distal tubule where aldosterone can stimulate further sodium reabsorption.

Other factors such as natriuretic peptide hormone can also affect sodium reabsorption. This hormone is secreted by the cardiac atria in response to atrial stretch following a rise in atrial pressure associated with, say, volume expansion. It is natriuretic (increases sodium excretion in urine) and, amongst other actions, reduces aldosterone concentration.

Sodium depletion

Inadequate oral intake of sodium is rarely the cause of sodium depletion, although inappropriate parenteral treatment may occasionally be implicated. Sodium depletion commonly occurs with water depletion, resulting in dehydration or volume depletion. The normal response of the body to the hypovolaemia includes an increase in aldosterone secretion (which stimulates renal sodium reabsorption) and an increase in ADH secretion if ECF volume depletion is severe.

The serum sodium level can give an indication of depletion, but it must be borne in mind that the serum sodium may be:

- increased, for example, where there is sodium and water loss but with predominant water loss, as occurs in excessive sweating;
- normal, for example, where there is isotonic sodium and water loss, as occurs from burns or a haemorrhage;
- decreased, for example, sodium loss with water retention as would occur if an isotonic sodium depletion were treated with a hypotonic sodium solution.

Sodium excess

Sodium excess can be due to either increased intake or decreased excretion. Excessive intake is not a common cause, although hypernatraemia can be associated with excessive intravenous saline infusion or unreplaced hypotonic water depletion, due to impaired access to free water or impaired thirst.

Sodium excess is usually due to impaired excretion. It may also be caused by a primary mineralocorticoid excess, for example, Cushing's syndrome or Conn's syndrome. However, it is often due to a secondary hyperaldosteronism associated with, for example, congestive cardiac failure, nephrotic syndrome, hepatic cirrhosis with ascites, or renal artery stenosis. Sodium and water retention causes oedema.

Hypernatraemia

The signs and symptoms of hypernatraemia include muscle weakness and confusion.

Drug-induced hypernatraemia is often the result of a nephrogenic diabetes insipidus-like syndrome whereby the renal tubules are unresponsive to ADH. The affected patient presents with polyuria, polydipsia or dehydration.

- Lithium and phenytoin are the most commonly implicated drugs. The diabetes insipidus-like syndrome with lithium has been reported after only 2 weeks of therapy. The syndrome is usually reversible on discontinuation. Whilst affected, however, many patients are unresponsive to exogenous ADH.
- Demeclocycline can also cause diabetes insipidus and can be used in the management of patients with the syndrome of inappropriate ADH secretion (SIADH).
- Phenytoin generally has a less pronounced effect on urinary volume than lithium or demeclocycline, and does not cause nephrogenic diabetes insipidus. It inhibits ADH secretion at the level of the central nervous system.

Hypernatraemia can be caused by a number of other drugs (Box 6.1) and by a variety of mechanisms; for example, hypernatraemia secondary to sodium retention is known to occur with corticosteroids whilst the administration of sodium-containing drugs parenterally in high doses also has the potential to cause hypernatraemia.

Hyponatraemia

A fall in the serum sodium level can be the result of sodium loss, water retention in excess of sodium usually resulting from defects in free water excretion due to low ECF volume or inappropriate secretion of ADH. Increased water intake may also contribute, or a combination of both factors. A number of drugs have also been implicated as causing hyponatraemia (Box 6.2).

The inappropriate secretion of ADH is the mechanism underlying many drug-induced hyponatraemias. In this syndrome, the drug may augment the action of endogenous ADH (e.g. chlorpropamide), increase the release of ADH (e.g. carbamazepine), or have a direct ADH-like action on the kidney (e.g. oxytocin or, more obviously, desmopressin). Hyponatraemia can also be induced by mechanisms different from those described above. Lithium may cause renal damage and a failure to conserve sodium. Likewise the natriuretic action of diuretics can predispose to hyponatraemia.

Box 6.1 Examples of drugs known to cause hypernatraemia

Adrenocorticotrophic hormone
Anabolic steroids
Androgens
Corticosteroids
Lactulose
Oestrogens
Oral contraceptives
Sodium bicarbonate

Box 6.2 Examples of drugs known to cause hyponatraemia

Amitriptyline and other tricyclic antidepressants
Amphotericin
Angiotensin converting enzyme inhibitors
Carbamazepine
Cisplatin
Clofibrate
Cyclophosphamide
Diuretics
Heparin
Lithium
Miconazole
NSAIDs
Opiates
Tolbutamide
Vasopressin
Vincristine

Potassium

The total amount of potassium in the body, like sodium, is 3000 mmol. About 10% of the body potassium is bound in red blood cells (RBCs), bone and brain tissue and is not exchangeable. The remaining 90% of total body potassium is free and exchangeable with the vast majority having an intracellular location, being pumped in and out by Na/K-ATPase pumps. This is controlled by mechanisms aimed at ensuring stable intracellular to extracellular ratios, and hence correct muscular and neuronal excitability. Only 2% of the exchangeable total body potassium is in the ECF, the compartment from where the serum concentration is sampled and measured. Consequently, the measurement of serum potassium is not an accurate index of total body potassium, but together with the clinical status of a patient it permits a sound practical assessment of potassium homeostasis.

The serum potassium concentration is controlled mainly by the kidney with the gastro-intestinal tract normally having a minor role. The potassium filtered in the kidney is almost completely reabsorbed in the proximal tubule. Potassium secretion is largely a passive process in response to the need to maintain membrane potential neutrality associated with active reabsorption of sodium in the distal convoluted tubule and collecting duct. The extent of potassium secretion is determined by a number of factors including:

- the amount of sodium available for exchange in the distal convoluted tubule and collecting duct;
- the availability of hydrogen and potassium ions for exchange in the distal convoluted tubule or collecting duct;
- the ability of the distal convoluted tubule or collecting duct to secrete hydrogen ions;
- the concentration of aldosterone;
- tubular fluid flow rate.

As described above, both potassium and hydrogen can neutralise the membrane potential generated by active sodium reabsorption and consequently there is a close relationship between potassium and hydrogen ion homeostasis. In acidosis, hydrogen ions are normally secreted in preference to

potassium and potassium moves out of cells, that is, hyperkalaemia is often associated with acidosis, except in renal tubular acidosis. In alkalosis, fewer hydrogen ions will be present and potassium moves into cells and potassium is excreted, that is, hypokalaemia is often associated with alkalosis.

The normal daily dietary intake of potassium is of the order of 60–200 mmol, which is more than adequate to replace that lost from the body. It is unusual for a deficiency in intake to account for hypokalaemia. A transcellular movement of potassium into cells, loss from the gut or excretion in the urine are the main causes of hypokalaemia.

Hypokalaemia

Transcellular movement into cells. The shift of potassium from the serum compartment of the ECF into cells accounts for the hypokalaemia reported following intravenous or, less frequently, nebulised administration of β-adrenoreceptor agonists such as salbutamol. Parenteral insulin also causes a shift of potassium into cells, and is used for this purpose in the acute management of patients with hyperkalaemia. Catecholamines, for example, adrenaline/epinephrine and theophylline also have this effect.

Loss from the gastro-intestinal tract. Although potassium is secreted in gastric juice, much of this, together with potassium ingested in the diet, is reabsorbed in the small intestine. Stools do contain some potassium, but in a patient with chronic diarrhoea or a fistula, considerable amounts of potassium may be lost and precipitate hypokalaemia. Likewise, the abuse of laxatives increases gastro-intestinal potassium loss and may precipitate hypokalaemia. Analogous to the situation with diarrhoea, the potassium secreted in gastric juice may be lost following persistent vomiting and can also contribute to hypokalaemia.

Loss from the kidneys. Mineralocorticoid excess, whether it be due to primary or secondary hyperaldosteronism or Cushing's syndrome, can increase urinary potassium loss and cause hypokalaemia. Likewise, increased excretion of potassium can result from renal tubular damage. Nephrotoxic antibiotics such as gentamicin have been implicated in this.

Many drugs which can induce hypokalaemia do so by affecting the regulatory role of aldosterone upon potassium–sodium exchange in the distal tubule and collecting duct. Administered corticosteroids mimic aldosterone and can, therefore, increase potassium loss.

The most commonly used groups of drugs that can cause hypokalaemia are thiazide and loop diuretics. Both groups of drugs increase the amount of sodium delivered and available for reabsorption at the distal convoluted tubule and collecting duct. Consequently, this will increase the amount of potassium excreted from the kidneys. Some of the drugs known to cause hypokalaemia are shown in Box 6.3.

Clinical features. The patient with moderate hypokalaemia may be asymptomatic, but the symptoms of more severe hypokalaemia include muscle weakness, hypotonia, paralytic ileus, depression and confusion. Arrhythmias may occur. Typical changes on the electrocardiogram (ECG) are of ST depression, T wave depression/inversion and prolonged P–R interval. Although hypokalaemia tends to make antiarrhythmic drugs less effective, the action of digoxin, in contrast, is potentiated leading to increased signs of toxicity. Insulin secretion in response to a rising blood glucose concentration requires potassium and this mechanism may be impaired in hypokalaemia. Rarely there may be impaired renal concentrating ability with polyuria and polydipsia.

Hypokalaemia is managed by giving either oral potassium or intravenous suitability dilute potassium solutions, depending on its severity and the clinical state of the patient.

Box 6.3 Examples of drugs known to cause hypokalaemia

- Amphotericin
- Aspirin
- Corticosteroids
- Diuretics
- Gentamicin
- Glucose
- Insulin
- Laxatives
- Penicillin G (sodium salt)
- Piperacillin + tazobactam
- Salicylates
- Sodium bicarbonate
- Sodium chloride
- Terbutaline
- Ticarcillin + clavulanic acid

Hyperkalaemia

Hyperkalaemia may arise from excessive intake, decreased elimination or shift of potassium from cells to the ECF. It is rare for excessive oral intake to be the sole cause of hyperkalaemia. The inappropriate use of parenteral infusions containing potassium is probably the most common iatrogenic cause of excessive intake. Hyperkalaemia is a common problem in patients with renal failure due to their inability to excrete a potassium load.

The combined use of potassium-sparing diuretics such as amiloride, triamterene or spironolactone with an angiotensin converting enzyme (ACE) inhibitor, which will lower aldosterone, is a recognised cause of hyperkalaemia, particularly in the elderly. Mineralocorticoid deficiency states such as Addison's disease where there is a deficiency of aldosterone also decrease renal potassium loss and contribute to hyperkalaemia. Those at risk of hyperkalaemia should be warned not to take dietary salt (NaCl) substitutes in the form of KCl.

The majority of body potassium is intracellular. Severe tissue damage, catabolic states or impairment of the energy-dependent sodium pump, caused by hypoxia or diabetic ketoacidosis, may result in apparent hyperkalaemia due to potassium moving out of and sodium moving into cells. If serum potassium rises, insulin release is stimulated which, through increasing activity in Na/K-ATPase pumps, causes potassium to move into cells. Box 6.4 gives examples of some drugs known to cause hyperkalaemia.

Box 6.4 Examples of drugs known to cause hyperkalaemia

Angiotensin converting enzyme inhibitors
Antineoplastic agents (cyclophosphamide, vincristine)
Non-steroidal anti-inflammatory drugs
β-Adrenoreceptor blocking agents
Ciclosporin
Digoxin (in acute overdose)
Diuretics, potassium sparing (amiloride, triamterene, spironolactone)
Heparin
Isoniazid
Lithium
Penicillins (potassium salt)
Potassium supplements
Tetracycline

Haemolysis during sampling or a delay in separating cells from serum will result in potassium escaping from blood cells into serum and causing an artefactual hyperkalaemia.

Clinical features. Hyperkalaemia can be asymptomatic but fatal. An elevated potassium level has many effects on the heart: notably the resting membrane potential is lowered and the action potential shortened. Characteristic changes of the ECG precede ventricular fibrillation and cardiac arrest.

In emergency management of a patient with hyperkalaemia (>6.5 mmol/L ± ECG changes), calcium gluconate (or chloride) at a dose of 10 mL of 10% solution is given intravenously over 5 min. This does not reduce the potassium concentration but antagonises the effect of potassium on cardiac tissue. Immediately thereafter, glucose 50 g with 20 units soluble insulin, for example, by intravenous infusion will lower serum potassium levels within 30 min by increasing the shift of potassium into cells.

If acidosis is present, bicarbonate administration may be considered.

The long-term management of hyperkalaemia may involve the use of oral or rectal polystyrene cation-exchange resins which remove potassium from the body. Chronic hyperkalaemia, in renal failure, is managed by a low potassium diet.

Calcium

The body of an average man contains about 1 kg of calcium and 99% of this is bound within bone. Calcium is present in serum bound mainly to the albumin component of protein (46%), complexed with citrate and phosphate (7%), and as free ions (47%). Only the free ions of calcium are physiologically active. Calcium metabolism is regulated by 1,25-dihydroxycholecalciferol (vitamin D) which, when serum calcium is low, is secreted to promote gastro-intestinal absorption of calcium, and by parathyroid hormone (PTH) which is inhibited by increased serum concentrations of calcium ions. PTH is secreted in response to low calcium concentrations and increases serum calcium by actions on osteoclasts, kidney and gut.

The serum calcium level is often determined by measuring total calcium, that is, that which is free and bound but the measurement of free or ionised calcium offers advantages in some situations.

In alkalosis, hydrogen ions dissociate from albumin, and calcium binding to albumin increases, together with an increase in complex formation. If the concentration of ionised calcium falls sufficiently, clinical symptoms of hypocalcaemia may occur despite the total serum calcium concentration being unchanged. The reverse effect, that is, increased ionised calcium, occurs in acidosis.

Changes in serum albumin also affect the total serum calcium concentration independently of the ionised concentration. A variety of equations are available to estimate the calcium concentration and many laboratories report total and adjusted calcium routinely. A commonly used formula is shown in Fig. 6.2. Caution must be taken when using such a formula in the presence of disturbed blood hydrogen ion concentrations.

Hypercalcaemia

Hypercalcaemia may be caused by a variety of disorders, the most common being primary hyperparathyroidism in which there is autonomous growth of PTH-producing cells and malignancy. Hypercalcaemia of malignancy is seen in multiple myeloma and carcinomas which metastasise in bone. It is also seen in squamous carcinoma of the bronchus, as a result of a peptide with PTH-like activity, produced by the tumour. Hypercalcaemia also occurs in thyrotoxicosis, vitamins A and D intoxication, acute renal failure, renal transplantation and acromegaly. PTH measurement can be pivotal in the establishment of the cause of hypercalcaemia.

Thiazide diuretics, lithium, tamoxifen and calcium supplements used in the management of osteoporosis are examples of some of the drugs which can cause hypercalcaemia.

An artifactual increase in total serum calcium may sometimes be seen as a result of a tourniquet being applied during venous sampling. The resulting venous stasis may cause redistribution of fluid from the vein into the extravascular space, and the temporary haemoconcentration will affect albumin levels.

Management of hypercalcaemia involves correction of any dehydration with normal saline followed by furosemide which inhibits tubular reabsorption of calcium. Bisphosphonates are used to inhibit bone turnover.

For albumin < 40 g/L:
Corrected calcium = [Ca] + 0.02 × (40 – [alb]) mmol/L
For albumin > 45 g/L:
Corrected calcium = [Ca] – 0.02 ([alb] – 45) mmol/L

Fig. 6.2 Formula for correction of total serum calcium concentration for changes in albumin concentration: albumin concentration = [alb] (albumin units = g/L); calcium concentration = [Ca] (total calcium units = mmol/L).

Hypocalcaemia

Hypocalcaemia can be caused by a variety of disorders including severe malnutrition, hypoalbuminaemia, hypoparathyroidism, pancreatitis and those that cause vitamin D deficiency, for example, malabsorption, reduced exposure to sunlight, liver disease and renal disease. In alkalaemia, which may occur when a patient is hyperventilating, there is an increase in protein binding of calcium, which can result in a fall in serum levels of ionised calcium, manifesting itself as paraesthesiae or tetany.

Drugs that have been implicated as causing hypocalcaemia include bisphosphonates which suppress formation and function of osteoclasts, phenytoin, phenobarbital, aminoglycosides, phosphate enemas, calcitonin, cisplatin, mithramycin and furosemide.

Biochemical measurements of serum calcium, phosphate and alkaline phosphatase can be normal in some patients with vitamin D deficiency and osteomalacia. The recent development of non-radioactive automated assays for serum PTH and 25-hydroxy vitamin D (25-OHD) has made measurement of these two hormones possible in many laboratories. There is a lack of consensus regarding a specific level of 25-OHD that is indicative of vitamin D deficiency, but this has usually been established by assessing the point at which serum PTH starts to rise. This, together with methodological and technical issues, prevents direct comparison of values across laboratories. Clinical decision limits for PTH and 25-OHD are laboratory specific and must be interpreted within the clinical context of each patient.

Phosphate

About 85% of body phosphate is in bone, 15% in ICF and only 0.1% in ECF. Its major function is in energy metabolism. Serum levels are regulated by absorption from the diet, which is partly under the control of vitamin D, and PTH which controls its excretion by the kidney and resorption from bone. The recent identification of genes encoding for renal phosphate transporters or associated proteins, and the discovery of a new hormone, fibroblast growth factor 23 and its emerging role in the bone–kidney axis which regulates systemic phosphate, has improved knowledge of homeostasis.

Hypophosphataemia

Clinical features. Severe hypophosphataemia can cause general debility, anorexia, anaemia, muscle weakness and wasting and some bone pain and skeletal wasting. As phosphorus is ubiquitous in various foods, inadequate dietary phosphorus intake requires near starvation. Refeeding of those recovering from energy depletion as a result, for example, of alcoholic bouts or diabetic ketoacidosis, without adequate provision of phophorus, can precipitate hypophosphataemia.

Hyperphosphataemia

Hyperphosphataemia occurs in chronic renal failure. Less common causes are secondary to rhabdomyolysis, tumour lysis or severe haemolysis. Hyperphosphataemia can cause hypocalcaemia. Treatment of hyperphosphataemia requires identification and correction of the underlying cause.

Magnesium

Magnesium is an essential cation, found primarily in bone, muscle and soft tissue. About 1% of the total body content is in the ECF. As an important cofactor for numerous enzymes and ATP, it is critical in energy requiring metabolic processes, protein synthesis, membrane integrity, nervous tissue conduction, neuromuscular excitability, muscle contraction, hormone secretion and in intermediary metabolism. Serum magnesium levels are usually maintained within a tight range (0.7–1.0 mmol/L). Although a serum concentration of less than this usually indicates some level of magnesium depletion, serum levels may be normal in spite of low intracellular magnesium due to magnesium depletion. Hypocalcaemia is a prominent manifestation of moderate to severe magnesium deficiency in humans.

Hypomagnesaemia is frequently seen in critically ill patients. Causes include excessive gastro-intestinal losses, renal losses, surgery, trauma, infection, malnutrition and sepsis. The drugs most likely to induce significant hypomagnesaemia are cisplatin, amphotericin B and ciclosporin, but it is also a potential complication of treatment with amikacin, gentamicin, laxatives, pentamidine, tobramycin, tacrolimus and carboplatin. A hypomagnesaemic effect of furosemide and hydrochlorothiazide is questionable and routine monitoring and treatment are not required. Use of digoxin has been associated with hypomagnesaemia, possibly by enhancing magnesium excretion, which may predispose to digoxin toxicity, for example, dysrhythmias.

Where treatment is indicated, oral supplements are available but because of their slow onset of action and gastrointestinal intolerance the intravenous route is often preferred and especially in critically ill patients with severe symptomatic hypomagnesaemia.

Hypermagnesaemia is most commonly caused by renal insufficiency and excess iatrogenic magnesium administration.

Creatinine

Serum creatinine concentration is largely determined by its rate of production, rate of renal excretion and volume of distribution. It is frequently used to evaluate renal function.

Creatinine is produced at a fairly constant rate from creatine and creatine phosphate in muscle. Daily production is a function of muscle mass and declines with age from 24 mg/kg/day in a healthy 25-year-old to 9 mg/kg/day in a 95-year-old. Creatinine undergoes complete glomerular filtration with little reabsorption by the renal tubules. Its clearance is, therefore, usually a good indicator of the glomerular filtration rate (GFR). As a general rule, and only at the steady state, if the serum creatinine doubles this equates to a 50% reduction in the GFR and consequently renal function. The serum creatinine level can be transiently elevated following meat ingestion, but less so than urea, or strenuous exercise. Individuals with a high muscle bulk produce more creatinine and, therefore, have a higher serum creatinine level compared to an otherwise identical but less muscular individual.

The value for creatinine clearance is higher than the true GFR due to the active tubular secretion of creatinine. In a patient with a normal GFR, this is of little significance. However, in an individual in whom the GFR is low (<10 mL/min), the tubular secretion may make a significant contribution to creatinine elimination and overestimate the GFR. In this type of patient, the breakdown of creatinine in the gut can also become a significant source of elimination. Some drugs including trimethoprim and cimetidine inhibit creatinine secretion, reducing creatinine clearance and elevating serum creatinine without affecting the GFR.

Measured and estimated GFR

GFR measured as the urinary or plasma clearance of an ideal filtration marker such as inulin is the best overall measure of kidney function but techniques are complex and expensive. Urinary clearance of creatinine allows estimation of GFR, but blood sampling and timed urine collection have practical difficulty and are subject to error.

In the steady state, the serum level of creatinine is related to the reciprocal of the GFR and estimating equations based on this, as well as age, sex, race and body size are in use to facilitate the detection, evaluation and management of chronic kidney disease. The Cockcroft Gault formula is not adjusted for body-surface area whereas the Modification of Diet in Renal Disease (MDRD) study equation is, and is more accurate in older and obese people. Estimates of GFR using these equations fall within the same interval for guiding dose adjustment of renally excreted drugs. Accuracy of estimates of GFR cannot be relied upon in patients with rapidly changing kidney function, those with unusual body habitus or diet, without chronic kidney disease and in patients with estimates of GFR of 60 mL/1.73 m^2 or greater.

Urea

The catabolism of dietary and endogenous amino acids in the body produces large amounts of ammonia. Ammonia is toxic and its concentration is kept very low by conversion in the liver to urea. Urea is eliminated in urine and represents the major route of nitrogen excretion. The urea is filtered from the blood at the renal glomerulus and undergoes significant tubular reabsorption of 40–50%. This tubular reabsorption is pronounced at low rates of urine flow but is reduced in advanced renal failure. Serum urea is a less reliable marker of GFR than creatinine. Urea levels vary widely with diet, rate of protein metabolism, liver production and the GFR. A high protein intake from the diet, tissue breakdown, major haemorrhage in the gut, and consequent absorption of the protein from the blood, and corticosteroid therapy may produce elevated serum urea levels (up to 10 mmol/L). Urea concentrations of more than 10 mmol/L are usually due to renal disease or decreased renal blood flow following shock or dehydration. As with serum creatinine levels, serum urea levels do not begin to increase until the GFR has fallen by 50% or more.

Production is decreased in situations where there is a low protein intake and in some patients with liver disease. Thus, non-renal as well as renal influences should be considered when evaluating changes in serum urea concentrations.

Arterial blood gases

Arterial blood gas analysis provides a rapid and accurate assessment of oxygenation, alveolar ventilation and acid–base status, the three processes which maintain pH homeostasis. The maintenance of arterial CO_2 tension ($PaCO_2$) depends on the quantity of CO_2 produced in the body and its removal through alveolar ventilation. High $PaCO_2$ (>6.1 kPa) indicates alveolar hypoventilation and low $PaCO_2$ (<4.5 kPa) implies alveolar hyperventilation.

The adequate delivery of oxygen to the tissues depends upon the cardiopulmonary system, arterial oxygen tension (PaO_2), oxygen concentration in inspired air and haemoglobin content and its affinity for oxygen. Oxygen saturation is measured by pulse oximetry or by arterial blood gas analysis. Hypoxaemia is defined as a PaO_2 of less than 12 kPa at sea level in an adult patient breathing room air.

Bicarbonate and acid–base

Bicarbonate acts as part of the carbonic acid–bicarbonate buffer system, which is important to maintain acid–base balance and thus the pH of the blood. pH homeostasis is accomplished through the interaction of lungs, kidneys and blood buffers. This interaction is best represented by the Henderson–Hasselbalch equation, an equation by which the pH of a buffer solution, blood plasma being one, can be determined (Fig. 6.3).

Plasma bicarbonate is controlled mainly by kidney and blood buffers. The lungs control the $PaCO_2$.

In metabolic acidosis such as that which occurs in renal failure, diabetic ketoacidosis or salicylate poisoning, bicarbonate levels fall. In metabolic alkalosis, the plasma bicarbonate concentration is high. This can occur, for instance, when there is a loss of hydrogen ions from the stomach, as in severe vomiting, or loss through the kidneys, as in mineralocorticoid excess or severe potassium depletion. In the latter situation, an increase in sodium reabsorption in the kidney results in bicarbonate retention and a loss of hydrogen ions. The blood buffer system of carbonic acid/bicarbonate base can act immediately to prevent excessive change in pH. The respiratory system takes a few minutes but the kidneys up to several days to readjust H^+ ions concentration.

$$pH = pKa + \text{Log}_{10} \frac{[HCO_3^-]}{\alpha\, pCO_2}$$

Fig. 6.3 The Henderson–Hasselbalch equation. pH, plasma pH; pK_a, negative log to base 10 of the apparent overall dissociation constant of carbonic acid; $[HCO_3^-]$, plasma bicarbonate concentration; α, solubility of carbon dioxide in blood at 37 °C; pCO_2, partial pressure of carbon dioxide in blood.

Glucose

The serum glucose concentration is largely determined by the balance of glucose moving into, and leaving, the extracellular compartment. In a healthy adult, this movement is capable of maintaining serum levels below 10 mmol/L, regardless of the intake of meals of varying carbohydrate content.

The renal tubules have the capacity to reabsorb glucose from the glomerular filtrate, and little unchanged glucose is normally lost from the body. Glucose in the urine (glycosuria) is normally only present when the concentration in serum exceeds 10 mmol/L, the renal threshold for total reabsorption.

Normal ranges for serum glucose concentrations are often quoted as non-fasting (<11.1 mmol/L) or fasting (3.3–6.0 mmol/L) concentration ranges. Fasting serum glucose levels between 6.1 and 7.0 mmol/L indicate impaired glucose tolerance. When symptoms are typical of diabetes, a fasting level above 7.0 mmol/L or a 2 h post-glucose or random serum glucose level ≥11.1 mmol/L is consistent with a diagnosis of diabetes. Other signs and symptoms, if present, are notably those attributable to an osmotic diuresis, and will suggest clinically the diagnosis of diabetes mellitus.

Glycated haemoglobin

Glucose binds to a part of the haemoglobin molecule to form a small glycated fraction. Normally, about 5% of haemoglobin is glycated, but this amount is dependent on the average blood glucose concentration over the lifespan of the red cells (about 120 days) and where red cell lifespan is reduced this leads to low glycated haemoglobin levels. The major component of the glycated fraction is referred to as HbA_{1C}.

Measurement of HbA_{1C} is well established as an indicator of chronic glycaemic control in patients with diabetes. Several methods exist for its determination, but the International Federation of Clinical Chemistry and Laboratory Medicine has recently approved a reference measurement procedure which is analytically specific. As a consequence, laboratories are moving over to measure the substance fraction of the valyl-I-fructosylated haemoglobin β-chains with the unit millimole per mole, and away from the non-specific HbA_{1C} as measured by various non-standardised laboratory procedures.

Uric acid

The production of uric acid, the end product of purine metabolism, is catalysed by xanthine oxidase, an enzyme linked to oxidative stress, endothelial dysfunction and heart failure. The purines, which are used for nucleic acid synthesis, are produced by the breakdown of nucleic acid from ingested meat or synthesised within the body.

Monosodium urate is the form in which uric acid usually exists at the normal pH of body fluids. The term urate is used to represent any salt of uric acid.

Two main factors contribute to elevated serum uric acid levels: an increased rate of formation and reduced excretion. Uric acid is poorly soluble and an elevation in serum concentration can readily result in deposition, as monosodium urate, in tissues or joints. Deposition usually precipitates an acute attack of gouty arthritis. The aim of treatment is to reduce the concentration of uric acid and prevent further attacks of gout. It has been hypothesised that measurement of urate could serve as a marker of cardiovascular risk because the serum uric acid level is an independent predictor of all causes of mortality in patients at high risk of cardiovascular disease, independent of diuretic use.

Liver function tests (LFTs)

Routine LFTs give information mainly about the activity or concentrations of enzymes and compounds in serum rather than quantifying specific hepatic functions and must be interpreted in the context of the patient's characteristic and the pattern of the abnormalities. Results are useful in confirming or excluding a diagnosis of clinically suspected liver disease, and monitoring its course.

Serum albumin levels and prothrombin time (PT) indicate hepatic protein synthesis; bilirubin is a marker of overall liver function.

Transaminase levels indicate hepatocellular injury and death, while alkaline phosphatase levels estimate the amount of impedance of bile flow.

Albumin

Albumin is quantitatively the most important protein synthesised in the liver, with 10–15 g/day being produced in a healthy man. About 60% is located in the interstitial compartment of the ECF, the remainder in the smaller, but relatively impermeable, serum compartment where it is present at a higher concentration. The concentration in the serum is important in maintaining its volume since it accounts for approximately 80% of serum colloid osmotic pressure. A reduction in serum albumin concentration often results in oedema.

Albumin has an important role in binding, among others, calcium, bilirubin and many drugs. A reduction in serum albumin will increase free levels of agents which are normally bound and adverse effects can result if the 'free' entity is not rapidly cleared from the body.

The serum concentration of albumin depends on its rate of synthesis, volume of distribution and rate of catabolism. Synthesis falls in parallel with increasing severity of liver disease or in malnutrition states where there is an inadequate supply of amino acids to maintain albumin production. Synthesis also decreases in response to inflammatory mediators such as interleukin. A low serum albumin concentration will occur when the volume of distribution of albumin increases, as happens, for example, in cirrhosis with ascites, in fluid retention states such as pregnancy or where a shift of albumin from serum to interstitial fluid causes dilutional hypoalbuminaemia after parenteral infusion of excess protein-free fluid. The movement of albumin from serum into interstitial fluid is often associated with increased capillary permeability in postoperative patients or those with septicaemia.

Other causes of hypoalbuminaemia include catabolic states associated with a variety of illnesses and increased loss of albumin, either in urine from damaged kidneys, as occurs in the nephrotic syndrome, or via the skin following burns or a skin disorder such as psoriasis, or from the intestinal wall in a protein-losing enteropathy. The finding of hypoalbuminaemia and no other alteration in liver tests virtually rules out hepatic origin of this abnormality.

Albumin's serum half-life of approximately 20 days precludes its use as an indicator of acute change in liver function but levels are of prognostic value in chronic disease.

An increase in serum albumin is rare and can be iatrogenic, for example, inappropriate infusion of albumin, or the result of dehydration or shock.

A shift of protein is known to occur physiologically when moving from lying down to the upright position. This can account for an increase in the serum albumin level of up to 10 g/L and can contribute to the variation in serum concentration of highly bound drugs which are therapeutically monitored.

Bilirubin

At the end of their life, RBCs are broken down by the reticuloendothelial system, mainly in the spleen. The haemoglobin molecules, which are subsequently liberated, are split into globin and haem. The globin enters the general protein pool, the iron in haem is reutilised, and the remaining tetrapyrrole ring of haem is degraded to bilirubin. Unconjugated bilirubin, which is water insoluble and fat soluble, is transported to the liver tightly bound to albumin. Unconjugated hyperbilirubinaemia in adults is most commonly the result of haemolysis, or Gilbert's syndrome due to genetic defects in UDP-glucronyltransferase. It is actively taken up by hepatocytes, conjugated with glucuronic acid and excreted into bile. The conjugated bilirubin is water soluble and secreted rapidly into the gut where it is broken down by bacteria into urobilinogen, a colourless compound, which is subsequently oxidised in the colon to urobilin, a brown pigment excreted in faeces. Some of the urobilinogen is absorbed and most is subsequently re-excreted in bile (enterohepatic circulation). A small amount is absorbed into the systemic circulation and excreted in urine, where it too may be oxidised to urobilin. The presence of increased conjugated bilirubin is usually a sign of liver disease.

The liver produces 300 mg of bilirubin each day. However, because the mature liver can metabolise and excrete up to 3 g daily, serum bilirubin concentrations are not a sensitive test of liver function. As a screening test they rarely do other than confirm the presence or absence of jaundice. In chronic liver disease, however, changes in bilirubin concentrations over time do convey prognostic information.

An elevation of serum bilirubin concentration above 50 µmol/L (i.e. approximately 2.5 times the normal upper limit) will reveal itself as jaundice, seen best in the skin and sclerae. Elevated bilirubin levels can be caused by increased production of bilirubin (e.g. haemolysis, ineffective erythropoiesis), impaired transport into hepatocytes (e.g. interference with bilirubin uptake by drugs such as rifampicin or due to hepatitis), decreased excretion (e.g. with drugs such as rifampicin and methyltestosterone, intrahepatic obstruction due to cirrhosis, tumours, etc.) or a combination of the above factors.

The bilirubin in serum is normally unconjugated, bound to protein, not filtered by the glomeruli and does not normally appear in the urine. Bilirubin in the urine (bilirubinuria) is usually the result of an increase in serum concentration of conjugated bilirubin and indicates an underlying pathological disorder.

Enzymes

The enzymes measured in routine LFTs are listed in Table 6.1. Enzyme concentrations in the serum of healthy individuals are normally low. When cells are damaged, increased amounts of enzymes are detected as the intracellular contents are released into the blood.

It is important to remember that the assay of 'serum enzymes' is a measurement of catalytic activity and not actual enzyme concentration and that activity can vary depending on assay conditions. Consequently, the reference range may vary widely between laboratories.

While the measurement of enzymes may be very specific, the enzymes themselves may not be specific to a particular tissue or cell. Many enzymes arise in more than one tissue and an increase in the serum activity of one enzyme can represent damage to any one of the tissues which contain the enzymes. In practice, this problem may be clarified because some tissues contain two or more enzymes in different proportions which are released on damage. For example, alanine and aspartate transaminase both occur in cardiac muscle and liver cells, but their site of origin can often be differentiated, because there is more alanine transaminase in the liver than in the heart. In those situations where it is not possible to look at the relative ratio of enzymes, it is sometimes possible to differentiate the same enzyme from different tissues. Such enzymes have the same catalytic activity but differ in some other measurable property, and are referred to as isoenzymes.

The measured activity of an enzyme will be dependent upon the time it is sampled relative to its time of release from the cell. If a sample is drawn too early after a particular insult to a tissue there may be no detectable increase in enzyme activity. If it is drawn too late, the enzyme may have been cleared from the blood.

Alkaline phosphatase

Alkaline phosphatase is an enzyme which transports metabolites across cell membranes. Alkaline phosphatases are found in the canalicular plasma membrane of hepatocytes, in bone where they reflect bone building or osteoblastic activity, and in the intestinal wall and placenta, kidneys and leucocytes. Each site of origin produces a specific isoenzyme of alkaline phosphatase, which can be electrophoretically separated if concentrations are sufficiently high. Hepatic alkaline phosphatase is present on the surface of bile duct epithelia.

Disorders of the liver which can elevate alkaline phosphatase include intra- or extra-hepatic cholestasis, space-occupying lesions, for example, tumour or abscess, and hepatitis. Drug-induced liver injury, for example, by ACE inhibitors or oestrogens, may present with a cholestatic pattern, that is, a preferential increase in alkaline phosphatase.

Physiological increases in serum alkaline phosphatase activity also occur in pregnancy due to release of the placental isoenzyme and during periods of growth in children and adolescents when the bone isoenzyme is released.

Pathological increases in serum alkaline phosphatase of bone origin may arise in disorders such as osteomalacia and rickets, Paget's disease of bone, bone tumours, renal bone disease, osteomyelitis and healing fractures. Alkaline phosphatase is also raised as part of the acute-phase response, for example, intestinal alkaline phosphatase may be raised in active inflammatory bowel disease. If in doubt, the origin of the enzyme can be indicated by assessment of γ-glutamyl transpeptidase (see next section) or electrophoresis to separate alkaline phosphatase isoenzymes.

Transaminases

The two transaminases of diagnostic use are aspartate transaminase (AST; also known as aspartate aminotransferase) and alanine transaminase (ALT; also known as alanine aminotransferase). These enzymes catalyse the transfer of α-amino groups from aspartate and alanine to the α-keto group of ketoglutaricacid to generate oxalacetic and pyruvic acid. They are found in many body tissues, with the highest concentration in hepatocytes and muscle cells. In the liver, ALT is localised solely in cytoplasm whereas AST is cytosolic and mitrochondrial.

Serum AST levels are increased in a variety of disorders including liver disease, crush injuries, severe tissue hypoxia, myocardial infarction, surgery, trauma, muscle disease and pancreatitis. ALT is elevated to a similar extent in the disorders listed which involve the liver, though to a lesser extent, if at all, in the other disorders. In the context of liver disease, increased transaminase activity indicates deranged integrity of hepatocyte plasma membranes and/or hepatocyte necrosis. They may be raised in all forms of viral and non-viral, acute and chronic liver disease, most markedly in acute viral, drug induced (e.g. paracetamol poisoning), alcohol related and ischaemic liver damage. Non-alcoholic fatty liver disease is now the most common cause of mild alteration of aminotransferase levels in the developed world.

γ-Glutamyl transpeptidase

γ-Glutamyl transpeptidase (Gamma GT; also known as γ-glutamyl transferase) is present in high concentrations in the liver, kidney and pancreas, where it is found within the endoplasmic reticulum of cells. It is a sensitive indicator of hepatobiliary disease but does not differentiate a cholestatic disorder from hepatocellular disease. It can also be elevated in alcoholic liver disease, hepatitis, cirrhosis and non-hepatic disease such as pancreatitis, congestive cardiac failure, chronic obstructive pulmonary disease and renal failure.

Serum levels of γ-glutamyl transpeptidase activity can be raised by enzyme induction by certain drugs such as phenytoin, phenobarbital, rifampicin and oral contraceptives.

Serum γ-glutamyl transpeptidase activity is usually raised in an individual with alcoholic liver disease. However, it can also be raised in heavy drinkers of alcohol who do not have liver damage, due to enzyme induction. Its activity can remain elevated for up to 4 weeks after stopping alcohol intake.

Although it lacks specificity, it has a high sensitivity for liver disease, and is thus useful for identifying the cause of a raised alkaline phosphatase level.

Ammonia

The concentration of free ammonia in the blood is very tightly regulated and is exceeded by two orders of magnitude by its derivative, urea. The normal capacity for urea production far exceeds the rate of free ammonia production by protein catabolism under normal circumstances, such that any increase in free blood ammonia concentration is a reflection of either biochemical or pharmacological impairment of urea cycle function or fairly extensive hepatic damage. Clinical signs of hyperammonaemia occur at concentrations >60 mmol/L and include anorexia, irritability, lethargy, vomiting, somnolence, disorientation, asterixis, cerebral oedema, coma and death; appearance of these findings is generally proportional to free ammonia concentration. Causes of hyperammonaemia include genetic defects in the urea cycle and disorders resulting in significant hepatic dysfunction. Ammonia plays an important role in the increase in brain water which occurs in acute liver failure. Measurement of the blood ammonia concentration in the evaluation of patients with known or suspected hepatic encephalopathy can help in diagnosis and assessing the effect of treatment. Valproic acid can induce hyperammonaemic encephalopathy as one of its adverse neurological effects.

Amylase

The pancreas and salivary glands are the main producers of serum amylase. The serum amylase concentration rises within the first 24 h of an attack of pancreatitis and then declines to normal over the following week. Although a number of abdominal and extra-abdominal conditions including loss of bowel integrity through infarction or perforation, chronic alcoholism, post-operative states and renal failure can result in a high amylase activity, in patients with the clinical picture of severe upper abdominal symptoms the specificity and sensitivity of an amylase level over 1000 IU/L in the diagnosis of pancreatitis is over 90%. There is a lack of prognostic significance of absolute values of amylase as values are directly related to the degree of pancreatic duct obstruction and inversely related to severity of pancreatic disease.

Cardiac markers

Troponins

Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are regulatory proteins that control the calcium-mediated interaction between actin and myosin in cardiac muscle. They are the preferred biomarker for myocardial necrosis as they have near absolute myocardial tissue specificity as well as high clinical sensitivity. The major international cardiac societies have introduced an international definition and classification for myocardial infarction which depends on the detection of a rise and/or fall (≥20%) of troponin with at least one value above the 99th percentile of the upper reference limit (URL) plus at least one of the following: (i) symptoms of ischaemia, or (ii) ECG evidence or imaging evidence of ischaemia. Sampling of cTn at two time points, usually admission and 12 h from worst pain, is usually needed, although if it is entirely clear that there has been a myocardial infarction, particularly in a late presentation, a second sample may not be needed. They contribute significantly to stratification of individuals with acute coronary syndromes, either alone or in combination with admission ECG or a predischarge exercise stress test. The decision as to whether to monitor cTnI or cTnT in a given laboratory is a balance between cost, availability of automated instrumentation and assay performance in which there is not yet standardisation between laboratories. Cardiac troponins offer extremely high tissue specificity and sensitivity but do not discriminate between ischaemic and non-ischaemic mechanisms of myocardial injury, such as myocarditis, cardiac surgery and sepsis. New, more sensitive assays are being developed, although studies will be required to define the clinical significance of minor releases of cTn and its relation to cardiac tissue viability.

Creatine kinase (CK)

CK is an enzyme which is present in relatively high concentrations in heart muscle, skeletal muscle and in brain in addition to being present in smooth muscle and other tissues. Levels are markedly increased following shock and circulatory failure, myocardial infarction and muscular dystrophies. Less marked increases have been reported following muscle injury, surgery, physical exercise, muscle cramp, an epileptic fit, intramuscular injection and hypothyroidism. The most important adverse effects associated with statins are myopathy and an increase in hepatic transaminases, both of which occur infrequently. Statin-associated myopathy represents a broad clinical spectrum of disorders, from mild muscle aches to severe pain and restriction in mobility, with grossly elevated CK levels. In rhabdomyolysis, a potentially life-threatening syndrome resulting from the breakdown of skeletal muscle fibres as a result of ischaemic crush injury, for example, large quantities of CK are measurable in the blood with the level of CK in the blood predicting the developments of acute renal failure. Medications and toxic substances that increase the risk of rhabdomyolysis are shown in Table 6.3.

Table 6.3 Medications and toxic substances that increase the risk of rhabdomyolysis

Direct myotoxicity	Indirect muscle damage
HMG-CoA reductase inhibitors, especially in combination with fibrate-derived lipid-lowering agents such as niacin (nicotinic acid) Ciclosporin Itraconazole Erythromycin Colchicine Zidovudine Corticosteroids	Alcohol Central nervous system depressants Cocaine Amphetamine Ecstasy (MDMA) LSD Neuromuscular blocking agents

HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LSD, lysergic acid diethylamide; MDMA, methylene dioxymethamphetamine.

CK has two protein subunits, M and B, which combine to form three isoenzymes, BB, MM and MB. BB is found in high concentrations in the brain, thyroid and some smooth muscle tissue. Little of this enzyme is present in the serum, even following damage to the brain. The enzyme found in serum of normal subjects is the MM isoenzyme which originates from skeletal muscle.

Cardiac tissue contains more of the MB isoenzyme than skeletal muscle. Following a myocardial infarction there is a characteristic increase in serum CK activity. Although measurement of activity of the MB isoenzyme was used in the past to detect myocardial damage, cardiac troponin measurement is now the preferred biomarker.

Lactate dehydrogenase (LD)

Lactate dehydrogenase has five isoenzymes (LD1–LD5). Total LD activity is rarely measured because of the lack of tissue specificity. Levels of activity are elevated following damage to the liver, skeletal muscle and kidneys, in both megaloblastic and immune haemolytic anaemias, and in intravascular haemolysis such as occurs in thrombotic thrombocytopenic purpura and paroxysmal nocturnal haemoglobinuria. In lymphoma, a high LD activity indicates a poor prognosis. Elevation of LD1 and LD2 occurs after myocardial infarction, renal infarction or megaloblastic anaemia; LD2 and LD3 are elevated in acute leukaemia; LD3 is often elevated in some malignancies; and LD5 is elevated after damage to liver or skeletal muscle.

Tumour markers

Tumour markers are defined as a qualitative or quantitative alteration or deviation from normal of a molecule, substance or process that can be detected by some type of assay above and beyond routine clinical and pathological evaluation. They may be detected within malignant cells, surrounding stroma or metastases, or as soluble products in blood,

secretions or excretions. In order to be useful clinically, the precise use of the marker in altering clinical management should have been defined by data based on a reliable assay, and a validated clinical outcome trial.

Whilst only a few markers contribute to the diagnosis of cancer, serial measurements can be useful in assessing the presence of residual disease and response to treatment. A detailed discussion of each marker, which include prostatic-specific antigen, human chorionic gonadotropin, α-fetoprotein, carcinoembryonic antigen, cancer antigen (CA125 and CA19) is outside the scope of this chapter. Updated National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for the use of tumour markers in the clinic were published in 2008 to encourage their optimal use. Use in predicting response to therapy and, therefore, targeting therapy is increasingly used: for breast cancer, oestrogen and progesterone receptors are mandatory for predicting response to hormone therapy, and human epidermal growth factor receptor-2 (HER2) measurement is mandatory for predicting response to trastuzumab.

Prostatic specific antigen (PSA) is a serine protease produced by normal and malignant prostatic epithelium and secreted into seminal fluid. Only minor amounts leak into the circulation from the normal prostate, but the release is increased in prostatic disease. It is not recommended for prostate cancer screening but is useful for the detection of recurrence and response to therapy. Free PSA measurement can improve distinguishing of malignant from benign prostatic disease when total PSA is <10 µcg/L, although results for free PSA differ between commercially available assay methods and require harmonisation.

Immunoglobulins

Immunoglobulins are antibodies which are produced by B lymphocytes. They are detected on elctrophoresis as bands in three regions: α, β and γ, with most occurring in the γ region. Hypergammaglobulinaemia may result from stimulation of B cells and produces an increased staining of bands in the γ region on electrophoresis. This occurs in infections, chronic liver disease and autoimmune disease.

In some diseases such as chronic lymphatic leukaemia, lymphoma and multiple myeloma, a discrete, densely staining band (paraprotein) can be seen in the γ region. In multiple myeloma, abnormal fragments of immunoglobulins are produced (Bence-Jones protein) which clear the glomerulus and are found in the urine.

Haematology data

The haematology profile is an important part of the investigation of many patients and not just those with primary haematological disease.

Typical measurements reported in a haematology screen, with their normal values, are shown in Table 6.4, whilst a list of the common descriptive terms used in haematology is presented in Table 6.5.

Table 6.4 Haematology data: typical normal adult reference values

Haemoglobin	11.5–16.5 g/dL
Red blood cell (RBC) count	3.8–4.8 × 10^{12}/L
Reticulocyte count	50–100 × 10^{9}/L
Packed cell volume (PCV)	0.36–0.46 L/L
Mean cell volume (MCV)	83–101 fL
Mean cell haemoglobin (MCH)	27–34 pg
Mean cell haemoglobin concentration (MCHC)	31.5–34.5 g/dL
White cell count (WBC)	4.0–11.0 × 10^{9}/L
Differential white cell count:	
Neutrophils (30–75%)	2.0–7.0 × 10^{9}/L
Lymphocytes (5–15%)	1.5–4.0 × 10^{9}/L
Monocytes (2–10%)	0.2–0.8 × 10^{9}/L
Basophils (<1%)	<0.1 × 10^{9}/L
Eosinophils (1–6%)	0.04–0.4 × 10^{9}/L
Platelets	150–450 × 10^{9}/L
Erythrocyte sedimentation rate (ESR)	1–35 mm/h
D-dimers	0–230 ng/mL
Ferritin	15–300 µcg/L
Total iron binding capacity (TIBC)	47–70 µmol/L
Serum B_{12}	170–700 ng/L
Red cell folate	160–600 µcg/l
Iron	11–29 µmol/L
Transferrin	1.7–3.4 g/L

RBC count

RBCs are produced in the bone marrow by the process of erythropoiesis. One of the major stimulants of this process is erythropoietin, produced mainly in the kidney. Immature erythroblasts develop into mature erythrocytes which are then released into the circulation:

erythroblasts
↓
normoblasts (nucleated)
↓
reticulocytes (non-nucleated)
↓
erythrocytes

Normally, only reticulocytes and non-nucleated mature erythrocytes are seen in the peripheral blood.

Table 6.5 Descriptive terms in common use in haematology

Anisocytosis	Abnormal variation in cell size (usually refers to RBCs), for example, red cells in iron deficiency anaemia
Agranulocytosis	Lack of granulocytes (principally neutrophils)
Aplastic	Depression of synthesis of all cell types in bone marrow (as in aplastic anaemia)
Basophilia	Increased number of basophils
Hypochromic	MCHC low, red cells appear pale microscopically
Leucocytosis	Increased white cell count
Leucopenia	Reduced white cell count
Macrocytic	Large cells
Microcytic	Small cells
Neutropenia	Reduced neutrophil count
Neutrophilia	Increased neutrophil count
Normochromic	MCHC normal; red cells appear normally pigmented
Pancytopenia	Decreased number of all cell types: it is synonymous with aplastic anaemia
Poikilocytosis	Abnormal variation in cell shape, for example, some red cells appear pear shaped in macrocytic anaemias
Thrombocytopenia	Lack of platelets

The lifespan of a mature red cell is usually about 120 days. If this is shortened, as for instance in haemolysis, the circulating mass of red cells is reduced and with it the supply of oxygen to tissues is decreased. In these circumstances, red cell production is enhanced in healthy bone marrow by an increased output of erythropoietin by the kidneys. Under normal circumstances red cells are destroyed by lodging in the spleen due to decreasing flexibility of the cells. They are removed by the reticuloendothelial system.

A high RBC (erythrocytosis or polycythaemia) indicates increased production by the bone marrow and may occur as a physiological response to hypoxia, as in chronic airways disease, or as a malignant condition of red cells such as in polycythaemia rubra vera.

Reticulocytes

Reticulocytes are the earliest non-nucleated red cells. They owe their name to the fine net-like appearance of their cytoplasm which can be seen, after appropriate staining, under the microscope and contains fine threads of ribonucleic acid (RNA) in a reticular network. Reticulocytes normally represent between 0.5% and 1.0% of the total RBC and do not feature significantly in a normal blood profile. However, increased production (reticulocytosis) can be detected in times of rapid red cell regeneration as occurs in response to haemorrhage or haemolysis. At such times the reticulocyte count may reach 40% of the RBC. The reticulocyte count may be useful in assessing the response of the marrow to iron, folate or vitamin B_{12} therapy. The count peaks at about 7–10 days after starting such therapy and then subsides.

Mean cell volume (MCV)

The MCV is the average volume of a single red cell. It is measured in femtolitres (10^{-15} L). Terms such as 'microcytic' and 'macrocytic' are descriptive of a low and high MCV, respectively. They are useful in the process of identification of various types of anaemias such as caused by iron deficiency (microcytic) or vitamin B_{12} or folic acid deficiency (megaloblastic or macrocytic).

Packed cell volume (PCV)

The PCV or haematocrit is the ratio of the volume occupied by red cells to the total volume of blood. It can be measured by centrifugation of a capillary tube of blood and then expressing the volume of red cells packed in the bottom as a percentage of the total volume. It is reported as a fraction of unity or as a percentage (e.g. 0.45% or 45%). The PCV is calculated nowadays as the product of the MCV and RBC. The PCV often reflects the RBC and will, therefore, be decreased in any sort of anaemia. It will be raised in polycythaemia. It may, however, be altered irrespective of the RBC, when the size of the red cell is abnormal, as in macrocytosis and microcytosis.

Mean cell haemoglobin (MCH)

The MCH is the average weight of haemoglobin contained in a red cell. It is measured in picograms (10^{-12} g) and is calculated from the relationship:

$$\text{MCH} = \frac{\text{Haemoglobin}}{\text{RBC}}$$

The MCH is dependent on the size of the red cells as well as the concentration of haemoglobin in the cells. Thus, it is usually low in iron-deficiency anaemia when there is microcytosis and there is less haemoglobin in each cell, but it may be raised in macrocytic anaemia.

Mean cell haemoglobin concentration (MCHC)

The MCHC is a measure of the average concentration of haemoglobin in 100 mL of red cells. It is usually expressed as grams per litre but may be reported as a percentage. The MCHC will be reported as low in conditions of reduced haemoglobin synthesis, such as in iron-deficiency anaemia. In contrast, in macrocytic anaemias the MCHC may be normal or only

slightly reduced because the large red cells may contain more haemoglobin, thus giving a concentration approximating that of normal cells. The MCHC can be raised in severe prolonged dehydration. If the MCHC is low, the descriptive term 'hypochromic' may be used (e.g. a hypochromic anaemia) whereas the term 'normochromic' describes a normal MCHC.

Haemoglobin

The haemoglobin concentration in men is normally greater than in women, reflecting in part the higher RBC in men. Lower concentrations in women are due, at least in part, to menstrual loss.

Haemoglobin is most commonly measured to detect anaemia. In some relatively rare genetic diseases, the haemoglobinopathies, alterations in the structure of the haemoglobin molecule can be detected by electrophoresis. Abnormal haemoglobins which can be detected in this manner include HbS (sickle haemoglobin in sickle cell disease) and HbA_2 found in β-thalassaemia carriers.

Platelets (thrombocytes)

Platelets are formed in the bone marrow. A marked reduction in platelet number (thrombocytopenia) may reflect either a depressed synthesis in the marrow or destruction of formed platelets.

Platelets are normally present in the circulation for 8–12 days. This is useful information when evaluating a possible drug-induced thrombocytopenia, since recovery should be fairly swift when the offending agent is withdrawn.

A small fall in the platelet count may be seen in pregnancy and following viral infections. Severe thrombocytopenia may result in spontaneous bleeding. A reduced platelet count is also found in disseminated intravascular coagulation, which manifests clinically as severe haemorrhages, particularly in the skin and results in rapid consumption of clotting factors and platelets.

An increased platelet count (thrombocytosis) occurs in malignancy, inflammatory disease and in response to blood loss.

White blood cell (WBC) count

White cells (leucocytes) are of two types: the granulocytes and the agranular cells. They are made up of various types of cells (Fig. 6.4) with different functions and it is logical to consider them separately. A haematology profile often reports a total white cell count and a differential count, the latter separating the composition of white cells into the various types.

Neutrophils

Neutrophils or polymorphonucleocytes (PMNs) are the most abundant type of white cell. They have a phagocytic function, with many enzymes contained in the lysosomal granules. They are formed in the bone marrow from the stem cells which form myoblasts and these develop through a number of stages into the neutrophil with a multiple-segmented nucleus. Neutrophils constitute approximately 40–70% of circulating white cells in normal healthy blood. Their lifespan is 10–20 days. The neutrophil count increases in the presence of infection, tissue damage (e.g. infarction) and inflammation (e.g. rheumatoid arthritis, acute gout). Neutropenia, also described as agranulocytosis in its severest forms, is associated with malignancy and drug toxicity, but may also occur in viral infections such as influenza, infectious mononucleosis and hepatitis.

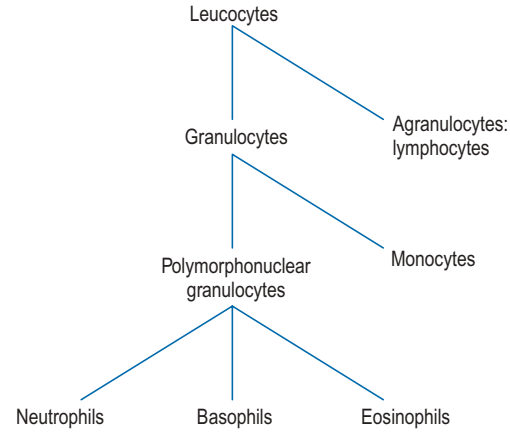

Fig. 6.4 Types of white cells.

Basophils

Basophils normally constitute a small proportion of the white cell count. Their function is poorly understood but basophilia occurs in various malignant and premalignant disorders such as leukaemia and myelofibrosis.

Eosinophils

Eosinophils constitute normally less than 6% of white cells. Their function appears to be concerned with inactivation of mediators released from mast cells, and eosinophilia is, therefore, apparent in many allergic conditions such as asthma, hay fever and drug sensitivity reactions as well as some malignant diseases.

Lymphocytes

Lymphocytes are the second most abundant white cells in the circulating blood, but the majority of them are found in the spleen and other lymphatic tissue. They are formed in the bone marrow. An increase in lymphocyte numbers occurs particularly in viral infections such as rubella, mumps, infectious hepatitis and infectious mononucleosis.

Monocytes

Monocytes are macrophages. Their numbers increase in some infections such as typhoid, subacute bacterial endocarditis, infectious mononucleosis and tuberculosis.

Other blood tests

Erythrocyte sedimentation rate (ESR)

The ESR is a measure of the settling rate of red cells in a sample of anticoagulated blood, over a period of 1 h, in a cylindrical tube.

In youth, the normal value is less than 10 mmol/h, but normal values do rise with age. The Westergren method, performed under standardised conditions, is commonly used in haematology laboratories. The ESR is strongly correlated with the ability of red cells to aggregate into orderly stacks or rouleaux. In disease, the most common cause of a high ESR is an increased protein level in the blood, such as the increase in acute-phase proteins seen in inflammatory disease. Proteins are thought to affect the repellent surface charges on red cells and cause them to aggregate into rouleaux and hence the sedimentation rate increases. Although some conditions may cause a low ESR, the test is principally used to monitor inflammatory disease. The ESR may be raised in the active phase of rheumatoid arthritis, inflammatory bowel disease, malignant disease and infection. The ESR is non-specific and, therefore, of little diagnostic value, but serial tests can be helpful in following the progress of disease, and its response to treatment.

C-reactive protein (CRP)

CRP, named for its capacity to precipitate the somatic C-polysaccharide of streptococcus pneumoniae, was the first acute-phase protein to be described. This non-specific acute-phase response occurs in animals in response to tissue damage, infection, inflammation and malignancy. Production of CRP is rapidly and sensitively upregulated, in hepatocytes, under the control of cytokine (IL-6) originating at the site of pathology. It recognises altered self and foreign molecules, as a result of which it activates complement and generates pro-inflammatory cytokines and activation of the adaptive immune system.

Serum concentrations rise by about 6 h, peaking around 48 h. The serum half-life is constant at about 19 h, so serum level is determined by synthesis rate, which therefore reflects the intensity of the pathological process stimulating this, and falls rapidly when this ceases. CRP values are not diagnostic, however, but can only be interpreted in knowledge of all other clinical and pathological results. In most diseases, the circulating value of CRP reflects ongoing inflammation or tissue damage more accurately than do other acute-phase parameters such as serum viscosity or the ESR. Drugs reduce CRP values by affecting the underlying pathology providing the acute-phase stimulus.

Coagulation

Coagulation is the process by which a platelet and fibrin plug is formed to seal a site of injury or rupture in a blood vessel. The current model of a 'coagulation network' differs from the previous popular cascade scheme. It proposes that blood coagulation is localised on the surfaces of activated cells in three overlapping steps: initiation, amplification and propagation. Coagulation is initiated when a tissue factor (TF) bearing cell is exposed to blood flow, following either damage of endothelium such as by perforation of a vessel wall or activation by chemicals, cytokines or the inflammatory process. The formation of a clot then involves a complex interaction between platelets and factor VIII bound to von Willebrand factor which leave the vascular space and adhere to collagen and other matrix components at the site of injury. The coagulation process is amplified when enough thrombin is generated on or near the TF bearing cells to trigger full activation of platelets and coagulation co-factors on the platelet surface. It ends with the generation of sufficient thrombin, to clot fibrinogen. To prevent inappropriate propagation of the thrombus, the process is controlled by naturally occurring anticoagulants and the fibrinolytic system, the final effector of which is plasmin which cleaves fibrin into soluble degradation products. The interaction between TF and factor VII is the most important in the initiation of coagulation and many of the coagulation reactions occur on the surface of cells (particularly platelets). The cellular model of normal haemostasis is shown in Fig. 6.5. Despite the complexity of this model, the basic coagulation tests can still be interpreted in relation to the 'intrinsic', 'extrinsic', and 'final common pathway' components of the traditional and previously held cascade (Fig. 6.6). The extrinsic pathway can be considered to consist of the factor VIIa/TF complex working with the factor Xa/Va complex and the intrinsic pathway to consist of factor XIa working with the complexes of factors VIIIa/IXa and factors Xa/Va. The extrinsic pathway operates on the TF bearing cell to initiate and amplify coagulation with the intrinsic pathway operating on the activated platelet surface to produce the burst of thrombin to form and stabilise the fibrin clot.

Monitoring anticoagulant therapy

The blood tests for the adequacy of the extrinsic pathway, prothombin time (PT) and the intrinsic pathway, activated partial thromboplastin time (aPTT) do not reflect the complexity of haemostasis in vivo, or the risk of bleeding. This requires interpretation of the result in the clinical context of surgical or accidental trauma or medical illness.

One stage PT

Measuring the PT is the most commonly used method for monitoring oral anticoagulation therapy. The PT is responsive to depression of three of the four vitamin K dependent factors (factors II, VII and X). The PT is measured by adding calcium and thromboplastin (a phospholipid-protein extract of tissue that promotes the activation of factor X by factor VIII) to citrated plasma.

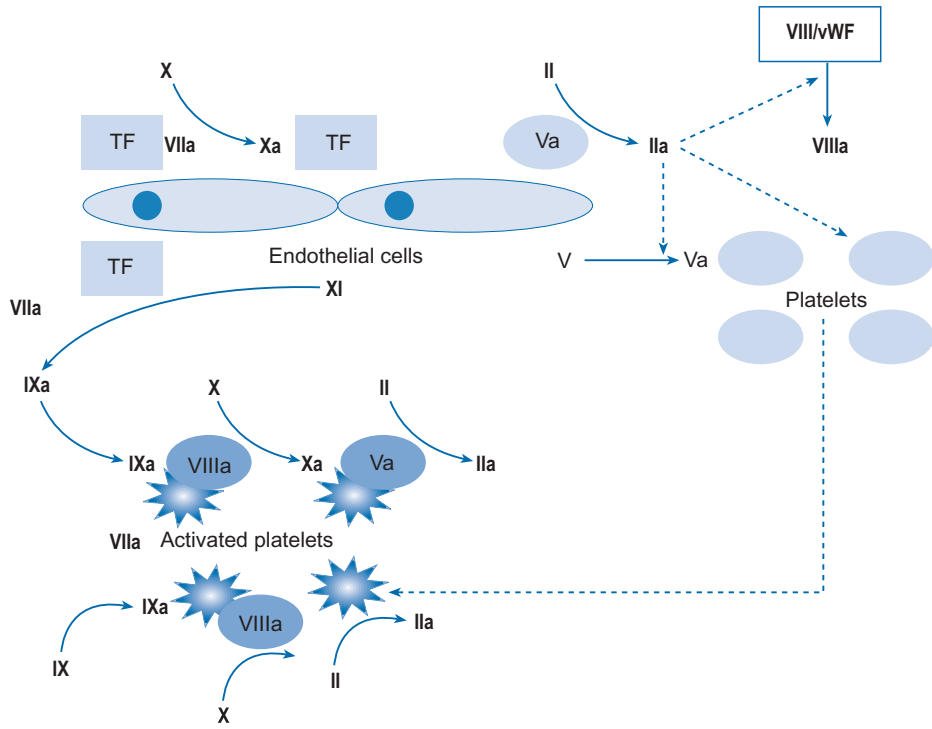

Fig. 6.5 Normal haemostasis; the cellular model.

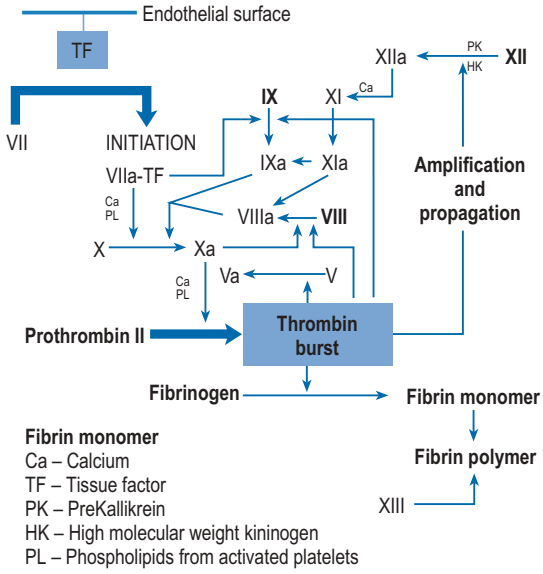

Fig. 6.6 Coagulation network.

International Normalised Ratio (INR)

The results of the test are commonly expressed as a ratio of the PT time of the patient compared with that of the normal control. This is known as the INR, a system used to standardise reporting worldwide.

$$\text{INR} = \left\{\frac{\text{Patient's PT}}{\text{Control PT}}\right\}^{\text{ISI}}.$$

The ISI is the international sensitivity index and represents the responsiveness of a given thromboplastin to the reduction of vitamin K dependent clotting factors and is allocated to commercial preparations of thromboplastin to standardise them. More responsive thromboplastins have lower ISI values.

The target value varies according to the indication for the anticoagulant, but for most, including for thrombo-embolic prophylaxis in atrial fibrillation, is 2.5. For some indications including recurrent deep vein thrombosis and pulmonary embolism whilst on warfarin, the target is higher at 3.5.

The most common use of the PT and INR is to monitor oral anticoagulant therapy, but the PT is also useful in assessing liver function because of its dependence on the activity of clotting factors I, II, V, VII and X which are produced in the liver. It may be prolonged also by deficiency in vitamin K, and consumptive coagulopathy. Obstructive jaundice may decrease the absorption of vitamin K and thereby increase PT. PT will respond to parenteral administration of vitamin K, which is ineffective when jaundice is caused by decreased functioning liver mass.

Activated partial thromboplastin time (APTT)

The APTT is the most common method for monitoring unfractionated heparin therapy.

A thromboplastic reagent is added to an activator such as activated silicone or kaolin. If the activator is kaolin, the test may be referred to as the PTTK (partial thromboplastin time kaolin) or the KCCT (kaolin–cephalin clotting time). Cephalin is a brain extract supplying the thromboplastin.

The mixture of thromboplastin and activator is mixed with citrated plasma to which calcium is added, and the time for the mixture to clot is recorded. The desirable APTT for optimal heparin therapy is between 1.5 and 2.5 times the normal control.

Low molecular weight heparins are effective and safe for the prevention and treatment of venous thromboembolism, and because they provide more predictable anticoagulant activity than unfractionated heparin it is usually not necessary to monitor the APTT during treatment. Laboratory monitoring using an anti-factor Xa assay may be of value in certain clinical settings, including patients with renal insufficiency, and use of fractionated heparin for prolonged periods in pregnancy or in newborns and children.

D-dimers

D-dimers are degradation products of fibrin clots, formed by the sequential action of three enzymes, thrombin, factor VIIIa and plasmin which degrades cross-linked fibrin to release fibrin degradation products and expose the D-dimer antigen. D-dimer assays measure an epitope on fibrin degradation products using monoclonal antibodies. As each has its own unique specificity, there is no standard unit of measurement or performance and clinicians need to be aware of that of their institution. Levels of D-dimers in the blood are raised in conditions associated with coagulation and are used to detect venous thromboembolism, although they are influenced by the presence of co-morbid conditions such as cancer, surgery and infectious diseases. D-dimer measurement has been most comprehensively validated in the exclusion of venous thromboembolism in certain patient populations and in the diagnosis and monitoring of coagulation activation in disseminated intravascular coagulation. More recently, assays are being used in the prediction of the risk of VTE recurrence. Diagnosis of DVT or PE should include a clinical probability assessment as well as D-dimer measurements. In patients with a low clinical probability of pulmonary embolism, a negative quantitative D-dimer test result effectively excludes PE. In suspected DVTs, D-dimer measurements combined with a clinical prediction score and compression ultrasonography study have a high predictive value.

Xanthochromia

Xanthochromia is a yellow discolouration of cerebrospinal fluid caused by haemoglobin catabolism. It is thought to arise within several hours of subarachnoid haemorrhage (SAH) and can help to distinguish the elevated red cell count observed after traumatic lumbar puncture from that observed following SAH, particularly if few red cells are present. Spectrophotometry to detect the presence of both oxyhaemoglobin and bilirubin, which both contribute to xanthochromia following SAH, is used, although some hospitals rely on visual inspection.

Iron, transferrin and iron binding

Iron is necessary for the functioning of all mammalian cells, but is particularly important in cells producing haemoglobin and myoglobin. Iron circulating in the serum is bound to transferrin. It leaves the serum pool and enters the bone marrow where it becomes incorporated into haemoglobin in developing red cells. Serum iron levels are extremely labile and fluctuate throughout the day and, therefore, provide little useful information about iron status.

Transferrin, a simple polypeptide chain with two iron binding sites, is the plasma iron binding protein which facilitates its delivery to cells bearing transferrin receptors. Measurement of total iron binding capacity (TIBC), from which the percentage of transferrin saturation with iron may be calculated, gives more information. Saturation of 16% or lower is usually taken to indicate an iron deficiency, as is a raised TIBC of greater than 70 µmol/L.

Ferritin is an iron storage protein found in cell cytosol. It acts as a depot, accepting excess iron and allowing for mobilisation of iron when needed. Serum ferritin measurement is the test of choice in patients suspected of having iron deficiency anaemia.

In normal individuals, the serum ferritin concentration is directly related to the available storage iron in the body. The serum ferritin level falls below the normal range in iron deficiency anaemia, and its measurement can provide a useful monitor for repletion of iron stores after iron therapy. Ferritin is an acute-phase protein and levels may be normal or high in the anaemia of chronic disease, such as occurs in rheumatoid arthritis or chronic renal disease.

Iron balance is regulated by hepcidin, a circulating peptide hormone, which aims to provide iron as needed, whilst avoiding excess iron promoting formation of toxic oxygen radicals.

Iron overload causes high concentrations of serum ferritin, as can liver disease and some forms of cancer. Genetic iron overload results from mutations in molecules which regulate hepcidin production or activity.

Vitamin B_{12} and folate

In the haematology literature, B_{12} refers not only to cyanocobalamin but also to several other cobalamins with identical nutritional properties. Folic acid, which can designate a specific compound, pteroylglutamic acid, is also more commonly used as a general term for the folates. Deficiency of cobalamin can result both in anaemia, usually macrocytic, and neurological disease, including neuropathies, dementia and psychosis. Folate deficiency produces anaemia, macrocytosis, depression, dementia and neural tube defects.

Liver disease tends to increase B_{12} levels, and they may be reduced in folate deficient patients: malabsorption of B_{12} may result from long-term ingestion of antacids such as proton-pump inhibitors or H_2-receptor antagonists or biguanides (metformin). Serum folate levels tend to increase in B_{12} deficiency, and alcohol can reduce levels. RBC folate is a better measure of folate tissue stores.

Current assays analyse total B_{12} concentration, only a small percentage of which is metabolically active. Varying test sensitivities and specificities result from the lack of a precise 'gold standard' for the diagnosis of cobalamin deficiency. In the future, new assays for the active component which is carried on holotranscobalamin may be of greater relevance if their clinical usefulness can be established.

Case studies

Case 6.1

Mr F is a 70-year-old man who presents with diffuse pains in his arms and legs. He is Asian, from Pakistan, and has been in England for 50 years.
He has the following biochemical test results:

Alkaline phosphatase	**436 U/L**
Total calcium	**2.27 mmol/L**
Ionised calcium	**1.10 mmol/L**
Phosphate	**0.97 mmol/L**
Vitamin D	**6 nmol/L**
Parathyroid hormone	**434 ng/L**
Urea	**4.6 mmol/L**
Creatinine	**63 μmol/L**

Questions

1. With respect to Mr F's blood results, what is the diagnosis?
2. How should he be treated?
3. How should he be monitored?

Answers

1. The diagnosis is osteomalacia due to vitamin D deficiency.
2. Vitamin D deficiency is caused by dietary deficiency of vitamin D and deficient endogenous production due to poor sunlight exposure. A deficit in activation can result from liver or kidney disease. People at high or low latitude, especially housebound, and people with dark coloured skin are at particular risk.
   Vitamin D_2 (cholecalciferol) or vitamin D_3 (ergocalciferol) is given orally in doses of 2000–4000 IU (0.05–0.1 mg) daily for 6–12 weeks, followed by daily supplements of 200–400 IU. The dose needed to achieve levels in the sufficient range sometimes requires daily doses over 800 IU. Where osteomalacia is due to intestinal malabsorption, higher doses of vitamin D and large doses of calcium may be required. In some instances, oral vitamin D is ineffective and the parenteral (intramuscular) route is required. In renal impairment, 1α hydroxylated vitamin D is usually prescribed.
3. Serum calcium should be monitored frequently during the first 1–2 months of therapy and less frequently once a stable dose has been established which has ensured return to normal of calcium, alkaline phosphatase and parathyroid hormone levels.

Case 6.2

A 70-year-old man on a hospital medical ward has a fast pulse rate and falling blood pressure. His recent drug history is warfarin as thrombo-embolic prophylaxis for chronic atrial fibrillation and erythromycin for a recent chest infection. He has vomited a moderate quantity of blood.

Haematology results:	**Hb 8.8 g/dL**
	RBC 4.7 × 10^{12}/L
Platelets	**570 × 10^9/L**
INR	**6.0**

MCV, MCH and the rest of the blood profile are normal

Clinical biochemistry:	**Urea 11.6 mmol/L**

Creatinine is normal and sodium and potassium concentrations are normal.

Questions

1. What is the cause of this patient's low haemoglobin?
2. What is the likely cause of his raised urea level?
3. What might have contributed to his over-anticoagulation as evidenced by his INR?

Answers

1. The cause of his low haemoglobin is a gastro-intestinal bleed. The picture is one of blood loss, manifested by a loss of red cells and haemoglobin. The red cells are of normal size and colour. As haemoglobin is normal immediately after a bleed, this man's bleed must have begun sufficiently long ago for haemodilution, through ingestion of fluid, to have occurred.
2. A raised urea in the presence of a normal creatinine may signify dehydration or gastro-intestinal bleeding. In this case, given the blood picture, the latter is more likely. Blood in the gastro-intestinal tract is a source of protein which will be absorbed into the hepatic portal system and converted to urea in the liver.
3. Erythromycin inhibits the cytochrome P450 system, particularly the CYP3A4 isoenzyme. CYP1A2 and CYP3A4 are the main enzymes for the inactivation of (R)-warfarin. Erythromycin, therefore, potentiates warfarin's action. The patient has been ill and in hospital and, therefore, his recent intake of vitamin K containing foods, for example, green leafy vegetables may well have been lower than is usual for him. Antibiotics can reduce synthesis of vitamin K by gut bacteria but this has little, if any, effect upon anticoagulation, and interactions with warfarin previously attributed to this mechanism have since been attributed to other modes of interaction.

Case 6.3

An 80-year-old patient with a history of Type II diabetes mellitus is admitted to hospital after an episode of vomiting and diarrhoea, followed by increasing confusion and drowsiness. His medication includes bendroflumethiazide and gliclazide. On examination he has a reduced level of consciousness, is dehydrated, and has a low blood pressure.
Biochemistry results show:

Sodium	**158 mmol/L**
Potassium	**4.6 mmol/L**
Urea	**44 mmol/L**
Creatinine	**250 μmol/L**
Random blood glucose	**38 mmol/L**

Arterial blood gases on air:

pH	**7.39**
pCO_2	**5.0 kPa**
Actual bicarbonate	**24 mmol/L**
pO_2	**12.7 kPa**

Questions

1. What is the diagnosis?
2. Why is the sodium raised?
3. What do his blood gases indicate?

Answers

1. The patient has hyperglycaemic hyperosmolar non-ketotic coma, evidenced by his clinical signs, raised blood glucose, sodium, urea and creatinine.

2. This is evidence of water depletion. This patient is dehydrated because of vomiting and diarrhoea, bendroflumethiazide and the osmotic diuresis caused by hyperglycaemia.
3. Normal serum pH and bicarbonate concentration show that he does not have metabolic ketoacidosis, the condition which only occurs in patients with Type I diabetes and which may be precipitated by infection.

Case 6.4

An 83-year-old man presents with a few weeks history of tiredness, unsteadiness and an abnormal sensation in both hands and feet. On examination he is ataxic with poor co-ordination due to absent joint position and vibration sense. Clinical diagnosis is of sensory ataxia due to dorsal column pathology. His drug treatment includes long-term metformin for Type 2 diabetes mellitus and lansoprazole.
Haematology results show:

Haemoglobin	**8.9 g/dL**
MCV	**110 fL**
B_{12}	**128 ng/L**
Red cell folate	**300 µcg/L**

Questions

1. What is the likely cause of this patient's symptoms and signs?
2. How should his neurological features be investigated?
3. What term describes this type of anaemia?
4. What drug treatment should he receive?

Answers

1. Subacute combined degeneration of the spinal cord and anaemia due to vitamin B_{12} deficiency.
2. Magnetic Resonance Imaging (MRI) of the spine. This is likely to show signal abnormality in the posterior columns of the spinal cord.
3. Macrocytic anaemia.
4. Parenteral administration, usually by intramuscular injection of vitamin B_{12}. In the UK, several loading doses are given followed by maintenance injections (e.g. 1000 µcg every 3 months) for the patient's lifetime. Treatment with pharmacological doses of oral cyanocobalamin is occasionally given, for example, if the patient has needle phobia or is allergic to the IM B_{12} preparation.

Further reading

Hoffbrand A.V., Moss P.A.H., Pettit, J.E. (Eds.), 2006. Essential Haematology, fifth ed. Blackwell, Oxford.

Gaw A. (Ed), 2008. Clinical Biochemistry: An Illustrated Colour Text, fourth ed. Churchill Livingstone, London.

7 Parenteral nutrition

S.J. Harwood and A.G. Cosslett

Key points

- Parenteral nutrition is indicated in people who are malnourished or at risk of malnutrition due to a non-functional, inaccessible or perforated gastro-intestinal tract or who have inadequate or unsafe enteral nutritional intake.
- Combinations of oral diet, enteral feeding and parenteral nutrition, either peripherally or centrally, may be appropriate.
- Parenteral nutrition regimens should be tailored to the nutritional needs of the patient and should contain a balance of seven essential components: water, L-amino acids, glucose, lipid with essential fatty acids, vitamins, trace elements and electrolytes.
- Advances in technology alongside expertise in pharmaceutical stability often permit the required nutrients to be administered from a single container. Increasingly, standard formulations are used, including licensed preparations.
- Parenteral nutrition must be compounded under validated aseptic conditions by trained specialists.
- Prescriptions are guided by baseline nutritional assessment, calculation of requirements using a range of algorithms, knowledge of the patient's disease status and ongoing monitoring.
- The incidence of complications with parenteral nutrition is reducing; knowledge of management is improving.

Introduction

Malnutrition

Malnutrition can be described as a deficiency, excess, or imbalance of energy, protein, and other nutrients that causes measurable adverse effects on body tissue, size, shape, composition, function and clinical outcome.

In UK hospitals, most malnutrition appears to be a general undernutrition of all nutrients (protein, energy and micronutrients) rather than marasmus (insufficient energy provision) or kwashiorkor (insufficient protein provision). Alternatively, there may be a specific deficiency, such as thiamine in severe hepatic disease.

Multiple causes may contribute to malnutrition. They may include inadequate or unbalanced food intake, increased demand due to clinical disease status, defects in food digestion or absorption, or a compromise in nutritional metabolic pathways. Onset may be acute or insidious.

Even mild malnutrition can result in problems with normal body form and function with adverse effects on clinical, physical and psychosocial status. Symptoms may include impaired immune response, reduced skeletal muscle strength and fatigue, reduced respiratory muscle strength, impaired thermoregulation, impaired skin barrier and wound healing. In turn, these predispose the patient to a wide range of problems including infection, delayed clinical recovery, increased clinical complications, inactivity, psychological decline and reduced quality of life. As symptoms may be non-specific, the underlying malnutrition may be left undiagnosed. Early nutrition intervention is associated with reduced average length of hospital stay and linked cost savings.

Nutrition screening

Routine screening is recommended by the Malnutrition Advisory Group of the British Association of Parenteral and Enteral Nutrition (BAPEN). This group has worked to promote awareness of the clinical significance of malnutrition and has produced guidelines to monitor and manage malnutrition. A range of screening criteria and tools have been developed and refined to assess nutritional status. Examples include the relatively simple and reproducible body mass index tool with consideration of other key factors (Table 7.1), and the BAPEN 'MUST' tool (Malnutrition Universal Screening Tool; BAPEN, 2003). Body weight should not be used in isolation; significant weight fluctuations may reflect fluid disturbances, and muscle wasting may be due to immobility rather than undernutrition. More complex anthropometry measurements are sometimes indicated to track changes.

Incidence of undernutrition

The incidence of undernutrition in hospitalised patients is not accurately known, although it is estimated as being between 20% and 40%.

Indications for parenteral nutrition (PN)

PN is a nutritionally balanced aseptically prepared or sterile physicochemically stable solution or emulsion for intravenous administration. It is indicated whenever the gastro-intestinal tract is inaccessible, perforated or non-functional or when enteral nutrition is inadequate or unsafe. PN should be considered if the enteral route is not likely to be possible for more

Table 7.1 Body mass index as a screening tool

BMI (kg/m²)	BMI category
<18.5	Underweight
18.5–25	Ideal BMI
25–29.9	Overweight
>30	Obese

Body mass index (BMI) = weight (kg)/height (m)²

than 5 days. PN may fulfill the total nutritional requirements or may be supplemental to an enteral feed or diet.

The simplest way to correct or prevent undernutrition is through conventional balanced food; however, this is not always possible. Nutritional support may then require oral supplements or enteral tube feeding. Assuming the gut is functioning normally, the patient will be able to digest and absorb their required nutrients. These include water, protein, carbohydrate, fat, vitamins, minerals and electrolytes; however, if the gut is not accessible or functioning adequately to meet the patient's needs, or gut rest is indicated, then PN may be used. While the enteral route is the first choice, this may still fail to provide sufficient nutrient intake in a number of patients. Complications and limitations of enteral nutrition need to be recognised.

A decision pathway can be followed to guide initial and ongoing nutritional support. While many are published, a locally tailored and regularly updated pathway is favoured. A useful starting point may be found at Fig. 7.1.

Close monitoring should ensure the patient's needs are met; a combination of nutrition routes is sometimes the best course. Where possible, patients receiving PN should also receive enteral intake, even minor gut stimulation has been linked with a reduction in the incidence of bacterial translocation through maintaining gut integrity and preventing overgrowth and cholestatic complications. PN should not be stopped abruptly but should be gradually reduced in line with the increasing enteral diet.

Nutrition support teams

A report published by the Kings Fund Report (1992) highlighted the issue of malnutrition both in the hospital and home setting. The findings led to the development of the British Association of Enteral and Parenteral Nutrition (BAPEN) and nutrition support teams throughout the UK. These multidisciplinary nutrition support teams comprise a doctor, nurse, pharmacist and dietitian. They function in a variety of ways, depending on the patient populations and resources. In general, they adopt either a consultative or an authoritative role in nutrition management. Many studies have shown their positive contribution to the total nutritional care of the patient through efficient and appropriate selection and monitoring of feed and route.

Components of a PN regimen

In addition to water, six main groups of nutrients need to be incorporated in a PN regimen (Table 7.2). The aim is to provide appropriate sources and amounts of all the equivalent building blocks in a single daily admixture.

Water volume

Water is the principal component of the body and accounts for approximately 60% and 55% of total body weight in men and women, respectively. Usually, homeostasis maintains appropriate fluid levels and electrolyte balance, and thirst drives the

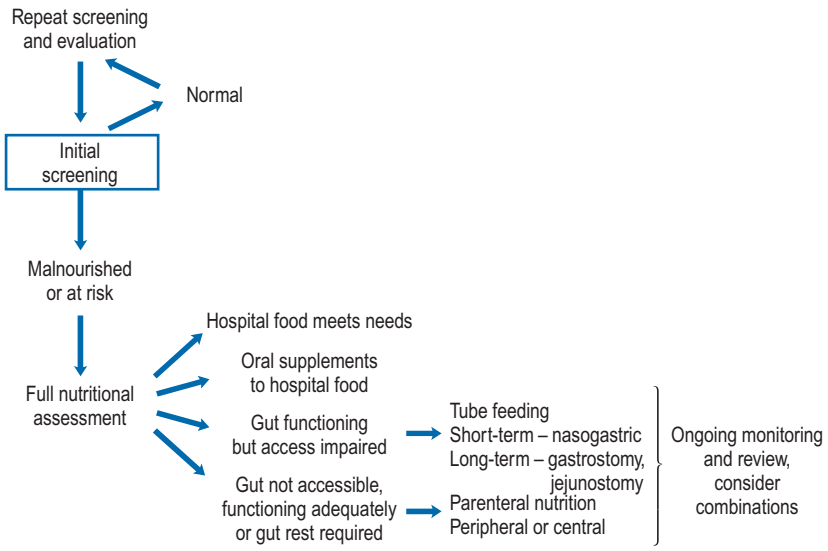

Fig. 7.1 Decision pathway to guide initial and ongoing nutritional support.

Table 7.2 Oral and equivalent parenteral nutrition source

Oral diet	Parenteral nutrition source
Water	Water
Protein	L-amino acids mixture
Carbohydrate	Glucose
Fat with essential fatty acids	Lipid emulsions with essential fatty acids
Vitamins	Vitamins
Minerals	Trace elements
Electrolytes	Electrolytes

healthy person to drink; however, some patients are not able physically to respond by drinking and so this homeostasis is ineffective. There is risk of over- or underhydration if the range of factors affecting fluid and electrolyte balance is not fully understood and monitored. In general, an adult patient will require 20–40 ml/kg/day fluid; however, Table 7.3 describes other factors that should be considered in tailoring input to needs.

Amino acids

Twenty L-amino acids are required for protein synthesis and metabolism, and the majority of these can be synthesised endogenously. Eight are called 'essential' amino acids because they cannot be synthesised (isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine). A further group of 'conditionally essential' amino acids (arginine, choline, glutamine, taurine and *S*-adenosyl-L-methionine) are defined as the patient's needs exceed synthesis in clinically stressed conditions. Also, due to the immature metabolic pathways of neonates, infants and children, some other amino acids are essential in the young patient, and these include histidine, proline, cysteine, tyrosine and taurine. Immature neonatal metabolism does not fully metabolise glycine, methionine, phenylalanine and threonine and so requirements are reduced.

To balance the patient's amino acid requirements and the chemical characteristics of the amino acids (solubility, stability and compatibility), a range of commercially available licensed solutions has been formulated containing a range of amino acid profiles (Table 7.4). Aminoplasmal®, Aminoven, Synthamin® and Vamin® are designed for adult patients. The amino acid profiles of Primene® and Vaminolact® are specifically tailored to neonates, infants and children (reflecting the amino acid profile of maternal cord blood and breast milk, respectively).

L-glutamine was initially excluded from formulations due to its low solubility and relatively poor stability in the aqueous environment; however, it is recognised that there is a clinical need for this amino acid in catabolic stress, and it is now available as an additive (Dipeptiven®) and as an amino acid solution containing a dipeptide form of glutamine (Glamin®) in which the peptide bond cleaves in the blood, releasing free L-glutamine. Research is also considering the rationale and merits of supplementing arginine, glutathione and ornithine α-ketoglutarate.

Table 7.3 Factors affecting fluid requirements

Consider increasing fluid input	Consider reducing fluid input
Signs/symptoms of dehydration	Signs/symptoms of fluid overload
Fever: increased insensible losses from lungs in hyperventilation and from skin in sweating. Allow 10–15% extra water per 10°C above normal	High humidity: reduced rate of evaporation
Acute anabolic state: increased water required for increased cell generation	Blood transfusion: volume input
High environmental temperature or low humidity: increased rate of evaporation	Cardiac failure: may limit tolerated blood volume
	Drug therapy: assess volume and electrolyte content of infused drug
Abnormal GI loss (vomiting, wounds, ostomies, diarrhoea): consider both volume loss and electrolyte content	
Burns or open wound(s): increased water evaporation	
	Renal failure: fluid may accumulate so reduce input accordingly or provide artificial renal support
Blood loss: assess volume lost and whether replaced by transfusion, colloid, crystalloid	

Table 7.4 Examples of amino acid and consequential nitrogen content of licensed amino acid solutions available in the UK

Name	Nitrogen content (g/L)	Electrolytes present
Aminoplasmal® 5% E	8	Potassium, magnesium, sodium and dihydrogen phosphate
Aminoplasmal® 10%	16	
Aminoven® 25	25.7	
Glamin®	22.4	
Hyperamine® 30	30	Sodium
Primene® 10%	15	
Synthamin® 9	9.1	Potassium, magnesium, sodium and acid phosphate
Synthamin® 9 EF	9.1	
Synthamin® 14	14	Potassium, magnesium, sodium and acid phosphate
Synthamin® 14 EF	14	
Synthamin® 17	17	Potassium, magnesium, sodium and acid phosphate
Synthamin® 17 EF	17	
Vamin® 9 Glucose	9.4	Potassium, magnesium, sodium and calcium
Vamin® 14	13.5	Potassium, magnesium, sodium and calcium
Vamin® 14EF	13.5	
Vamin® 18EF	18	
Vaminolact®	9.3	

For adults, PN solutions are generally prescribed in terms of the amount of nitrogen they provide, rounding to the nearest gram; for example, 9, 11, 14 or 18 g nitrogen regimens may be prescribed. Assuming adequate energy is supplied, most adult patients achieve nitrogen balance with approximately 0.2 g nitrogen/kg/day, although care should be taken with overweight patients.

A 24-h urine collection can be used as an indicator of nitrogen loss, assuming all urine is collected and urea or volume output is not compromised by renal failure; however, a true nitrogen output determination requires measurement of nitrogen output from all body fluids, including urine, sweat, faeces, skin and wounds. Nitrogen balance studies can indicate the metabolic state of the patient (positive balance in net protein synthesis, negative balance in protein catabolism). Urinary urea constitutes approximately 80% of the urinary nitrogen. The universally accepted conversion factor for nitrogen to protein is 1 g nitrogen per 6.25 g of protein.

Amino acid solutions are hypertonic to blood and should not be administered alone into the peripheral circulation.

Energy

Many factors affect the energy requirement of individual patients and these include age, activity and illness (both severity and stage). Predictive formulae can be applied to estimate the energy requirement, for example, the Harris Benedict equation or the more commonly used Schofield equation, which is shown below in Table 7.5.

Alternatively, calorimetry techniques can be used; however, no single method is ideal or suits all scenarios. Often it is found that two methods result in different recommendations. The majority of adults can be appropriately maintained on 25–35 non-protein kcal/kg/day. There is debate over whether to include amino acids as a source of calories since it is simplistic to assume they are either all spared for protein synthesis or fed into the metabolic pathways (Krebs cycle) and contribute to the release of energy-rich molecules. In general, we refer to 'non-protein energy' and sufficient lipid and glucose energy is supplied to spare the amino acids. As a rough guide, the non-protein energy-to-nitrogen ratio is approximately 150:1, although an ideal ratio for all patients has not been absolutely defined. A lower ratio is considered for critically ill patients, while higher ratios are considered for less catabolic patients.

Dual energy

In general, energy should be sourced from a balanced combination of lipid and glucose; this is termed 'dual energy' and is more physiological than an exclusive glucose source. Typically, the fat-to-glucose ratio remains close to the 60:40–40:60 ranges.

Dual energy can minimise the risk of giving too much lipid or glucose since complications increase if the metabolic capacity of either is exceeded. A higher incidence of acute adverse

Table 7.5 Schofield equation

Age (years)	Male	Female
15–18	BMR = 17.6 × weight (kg) + 656	BMR = 13.3 × weight (kg) + 690
18–30	BMR = 15.0 × weight (kg) + 690	BMR = 14.8 × weight (kg) + 485
30–60	BMR = 11.4 × weight (kg) + 870	BMR = 8.1 × weight (kg) + 842
>60	BMR = 11.7 × weight (kg) + 585	BMR = 9.0 × weight (kg) + 656

BMR, basal metabolic rate.

effects is noted with faster infusion rates and higher total daily doses, especially in patients with existing metabolic stress. It is, therefore, essential that the administered dose complements the energy requirements and the infusion rate does not exceed the metabolic capacity.

While effectively maintaining nitrogen balance, lipid inclusion is seen to confer a number of advantages (Box 7.1). Some patients, notably long-term home patients, do not tolerate daily lipid infusions and need to be managed on an individual basis. Depending on the enteral intake and nutritional needs, lipids are prescribed for a proportion of the days. A trial with the newer generation lipid emulsions may be appropriate.

Glucose

Glucose is the recommended source of carbohydrate (1 g anhydrous glucose provides 4 kcal). Table 7.6 indicates the energy provision and tonicity for a range of concentrations. Glucose 5% is regarded as isotonic with blood. The higher concentrations cause phlebitis if administered directly to peripheral veins and should, therefore, be given by a central vein or in combination with compatible solutions to reduce the tonicity.

The glucose infusion rate should generally be between 2 and 4 mg/kg/min. An infusion of 2 mg/kg/min (equating to approximately 200 g (800 kcal) per day for a 70 kg adult) represents the basal glucose requirement, whereas 4 mg/kg/day is regarded as the physiological optimal rate. Higher levels are tolerated by some patients especially those at home on PN, but monitoring of blood glucose is required at least initially. Care needs to be taken as glucose oxidation occurs, but there is an increased conversion to glycogen and fat. If excess glucose is infused and the glycogen storage capacity exceeded, the circulating glucose level rises, *de novo* lipogenesis occurs (production of fat from glucose) and there is an increased incidence of metabolic complications.

Box 7.1 Examples of the advantages of dual energy systems over glucose-only energy systems

Minimise risk of hyperglycaemia and related complications
Prevent and reverse fatty liver (steatosis)
Reduce carbon dioxide production and respiratory distress
Meet higher calorie requirements of septic and trauma patients when glucose oxidation reduced and lipid oxidation increased
Reduce metabolic stress
Support immune function
Improve lean body mass and reduce water retention
Permit peripheral administration, through reduced tonicity
Facilitate fluid restriction, as lipid is a concentrated source of energy
Are a source of essential fatty acids, preventing and correcting deficiency

Table 7.6 Energy provision and tonicity of glucose solutions

Concentration (w/v)	Energy content (kcal/L)	Osmolarity (mOsmol/L)
5%	200	278
10%	400	555
20%	800	1110
50%	2000	2775
70%	2800	3885

Lipid emulsions

Lipid emulsions are used as a source of energy and for the provision of the essential fatty acids, linoleic and alpha-linolenic acid. Supplying 10 kcal energy per gram of lipid, they are energy rich and can be infused directly into the peripheral veins since they are relatively isotonic with blood.

Typically, patients receive up to 2.5 g lipid/kg/day. For practical compounding reasons, and assuming clinical acceptance, this tends to be rounded to 100 g or 50 g. Details of lipid emulsions available within the UK can be found in Table 7.7.

Lipid emulsions are oil-in-water formulations. Figure 7.2 shows the structure of triglycerides (three fatty acids on a glycerol backbone) and a lipid globule, stabilised at the interface by phospholipids. Ionisation of the polar phosphate group of the phospholipid results in a net negative charge of the lipid globule and an electromechanically stable formulation. The lipid globule size distribution is similar to that of the naturally occurring chylomicrons (80–500 nm), as indicated in Fig. 7.3.

The first-generation lipid emulsions have been in use since the 1970 s and utilise soybean oil as the source of long chain fatty acids. More recent research on lipid metabolic pathways and clinical outcomes has indicated that the fatty acid profile of soybean oil alone is not ideal. For example, it is now recognised that these lipid emulsions contain

Table 7.7 Examples of licensed lipid emulsions available in the UK

Lipid emulsion type	Details of products with kJ per litre
Soybean oil	Intralipid® 10% (4600), 20% (8400), 30% (12600)
Purified olive oil/soybean oil	ClinOleic® 20% (8360)
Medium chain triglycerides/ soybean oil	Lipofundin® MCT/LCT 10% (4430), 20% (8000)
Purified structured triglycerides	Structolipid® 20% (8200)
Omega-3-acid triglycerides/ soybean oil/medium chain triglycerides	Lipidem® (7900)
Highly refined fish oil	Omegaven® (4700)
Fish oil/olive oil/soybean oil/ medium chain triglycerides	SMOFLipid® (8400)

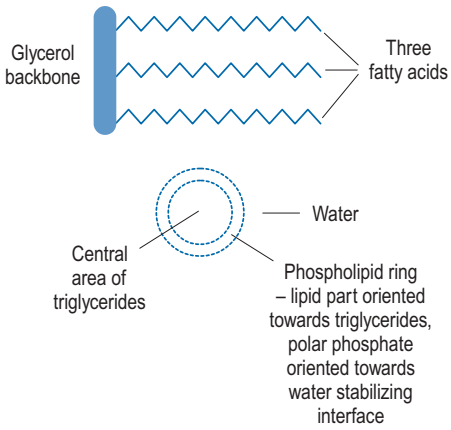

Fig. 7.2 Triglyceride structure and composition of lipid emulsion globule.

excess essential polyunsaturated fatty acids, resulting in a qualitative and quantitative compromise to the eicosanoid metabolites that have important roles in cell structure, haemodynamics, platelet function, inflammatory response and immune response.

The molecular structure of the fatty acids has an important impact on the patient's oxidative stress. Two strategies have been applied to overcome this: a reduction in the polyunsaturated fatty acid content through an improved balance of fatty acids or the inclusion of medium chain fatty acids. This has resulted in the development of lipid emulsions that include olive oil (rich in monounsaturated oleic acid and antioxidant α-tocopherol with an appropriate level of essential polyunsaturated fatty acids), fish oil (rich in omega 3 fatty acids) and medium chain triglycerides or structured triglycerides (reduced long chain fatty acid content). Clinical application of these newer lipid emulsions depends upon good clinical studies within the relevant patient population. Such studies should evaluate the efficacy of energy provision and clinical tolerance and report improvements in the eicosanoid-dependent functions or oxidative stress.

Both egg and soybean phospholipids include a phosphate moiety. There is a debate as to whether this is bioavailable. Therefore, some manufacturers include the phosphate content in their stability calculations, while others do not.

The 20% lipid emulsions are favoured, especially in paediatrics, as they contain less phospholipid than the 10% emulsions in relation to triglyceride provision. If there is incomplete clearance of the infused phospholipids, lipoprotein X, an abnormal phospholipid-rich low-density lipoprotein, is generated and a raised blood cholesterol observed. The incidence of raised lipoprotein X levels is greater with the 10% emulsions as they present proportionally more phospholipid.

Lipid clearance monitoring is particularly important in patients who are at risk of impaired clearance, including those who are hyperlipidaemic, diabetic, septic, have impaired renal or hepatic function or are critically ill (Crook, 2000).

Micronutrients

Micronutrients have a key role in intermediary metabolism, as both co-factors and co-enzymes. For example, zinc is required by over 200 enzyme systems and affects many diverse body functions including acid–base balance, immune function and nucleic acid synthesis. It is evident, therefore, that the availability of micronutrients can affect enzyme activity and total metabolism. When disease increases the metabolism of the major substrates, the requirement for micronutrients is increased. Some of the micronutrients also play an essential role in the free radical scavenging system. These include the following:

- copper, zinc and manganese, in the form of superoxide dismutase, dispose of superoxide radicals
- selenium, in the form of glutathione peroxidase, removes hydroperoxyl compounds
- vitamin C is a strong reducing agent
- vitamins A, E and ß-carotene react directly with free radicals

By the time a patient starts PN, they may have already developed a deficiency of one or more essential nutrients. By the time a specific clinical deficiency is observed, for example,

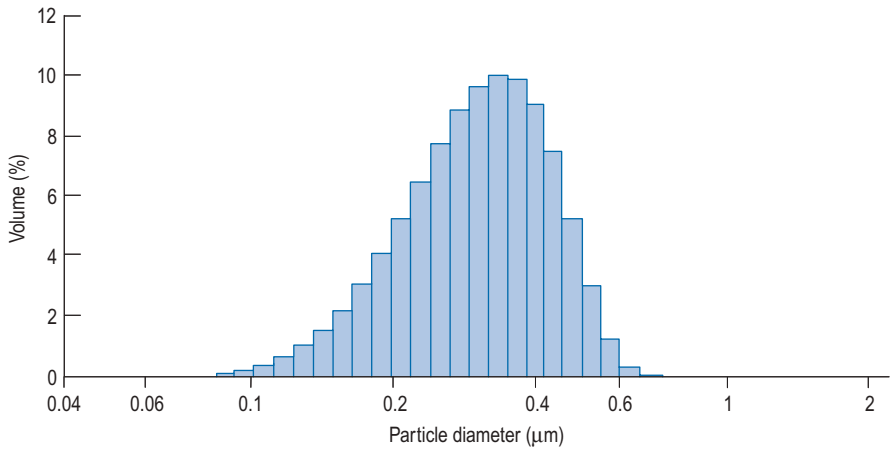

Fig. 7.3 Lipid globule size distribution curve of Ivelip® 20%.

Box 7.2 Factors affecting micronutrient requirements

Baseline nutritional state on starting parenteral nutrition
- Acute or chronic onset of illness
- Dietary history
- Duration and severity of inadequate nutritional intake

Increased loss
- Small bowel fistulae/aspirate: rich in zinc
- Biliary fluid loss: rich in copper
- Burn fluid loss: rich in zinc, copper, selenium

Increased requirement
- Increased metabolism: acute in anabolic phase following catabolic phase of critically ill
- Active growth

Organ function
- Liver failure: copper and manganese clearance reduced
- Renal failure: aluminium, chromium, zinc and nickel clearance reduced

depigmentation of hair in copper deficiency or skin lesions in zinc deficiency, the patient will already have tried to compensate to maintain levels, compromised intracellular enzyme activity and antioxidant systems and expressed non-specific symptoms such as fatigue and impaired immune response. A summary of factors that affect micronutrient needs is presented in Box 7.2.

Measuring blood levels of vitamins and trace elements in acutely ill patients is of limited value. It is recommended that these are measured every 1–6 months depending on levels, and in patients at home on PN (NICE, 2006). Deficiency states are clinically significant but, with non-specific symptoms, they are often difficult to diagnose.

Micronutrient experts prefer to prevent a deficit developing and compromising the clinical state, rather than perform regular monitoring of blood results.

Micronutrients should be included daily from the start of the PN. The requirements are increased during critical illness and in chronically depleted patients. Patients with major burns and trauma or with artificial renal support can quickly become depleted. Their supplementation may influence the outcome of the disease. Even if the patient has reasonable levels and reserves initially, they can quickly become depleted if they are not supported by daily administration. Additional oral or enteral supplements may be considered if there is some intestinal absorption. However, copper deficiency can increase iron absorption and zinc intake can decrease copper absorption.

The micronutrients naturally fall into two groups: the trace elements and vitamins. Micronutrients should be added to all PN infusions under appropriate, controlled, environmental conditions prior to administration (NICE, 2006).

Trace elements

Trace elements are generally maintained at a relatively constant tissue concentration and are present to a level of less than 1 mg/kg body weight. They are essential; deficiency results in structural and physiological disorders which, if identified early enough, can be resolved by re-administration. Ten essential trace elements are known: iron, copper, zinc, fluorine, manganese, iodine, cobalt (or as hydroxycobolamin), selenium, molybdenum and chromium. Adult reference ranges for daily requirements of trace metals can be found in Table 7.8. Currently two preparations are commercially available for adults (Decan®, Additrace®) together with a single paediatric preparation (Peditrace®).

Various recommended baseline doses have been published but no single licensed preparation provides all trace elements at the dose required. Concern over neurotoxicity with accumulated manganese, especially in liver failure, led to a reduction in the advised daily dose and recommendations for plasma monitoring. Recognising the benefits of zinc and selenium on the free radical scavenging system, some specialists advise an increase in the administered dose. Some patients, notably those with burns, renal replacement therapy and/or multiple trauma, as well as long-term patients, may require extra trace elements (Fleming, 1989).

Vitamins

There are two groups of vitamins: the water-soluble vitamins and the fat-soluble vitamins. Fat-soluble vitamins are stored in the body fat, whereas excess water-soluble vitamins are renally cleared; therefore, if there is inadequate provision, deficiency states for the water-soluble vitamins reveal themselves first. The adult reference range for daily requirements of vitamins can be found in Table 7.9. Commercially available preparations are Solivito® N (water soluble), Vitlipid® N Adult/Infant (fat soluble), Cernevit® (water and fat soluble).

In an attempt to reduce the risk of osteoporosis, especially in home PN patients, there have been recent changes to recommended biochemical vitamin D levels (Holick, 2007). Patients on long-term PN should have vitamin D levels measured

Table 7.8 Adult daily reference range for trace elements

Sex	Age	Iron (μmol/day)	Zinc (μmol/day)	Copper (μmol/day)	Selenium (μmol/day)
Male	19–50+	160	145	19	0.9
Female	19–50	260	110	19	0.8
Female	50+	160	110	19	0.8

Table 7.9 Adult daily reference ranges for vitamins (adapted from Department of Health, 1991)

Sex	Age	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin (mg/day)	Vit B6 (mg/day)	Vit B12 (µcg/day)	Folate (µcg/day)	Vit C (mg/day)	Vit A (µcg/day)	Vit D (µcg/day)
Male	19–50	1.0	1.3	17	1.4	1.5	200	40	700	–
Male	50+	0.9	1.3	16	1.4	1.5	200	40	700	–[a]
Female	19–50	0.8	1.1	13	1.2	1.5	200	40	600	–
Female	50+	0.8	1.1	12	1.2	1.5	200	40	600	–[a]

[a] After age 65, the recommended normal daily intake is 10µcg/day for male and females.

every 6 months. If low, this should be supplemented in order to help protect against osteoporosis which is a well recognised complication of home PN.

Electrolytes

Electrolytes are included to meet the patient's needs. Typical daily parenteral requirements are

- sodium (1–1.5 mmol/kg)
- potassium (1–1.5 mmol/kg)
- calcium (0.1–0.15 mmol/kg)
- magnesium (0.1–0.2 mmol/kg)
- phosphate (0.5–0.7 mmol/kg).

Depending upon the stability of the patient's clinical state, they are kept relatively constant or adjusted on a near daily basis, reflecting changes in blood biochemistry. Tables, for example, British National Formulary can be used to guide electrolyte replacement if there is excessive gastro-intestinal waste or high losses through burns. Hypophosphataemia should be corrected before starting parenteral or enteral nutrition to avoid the refeeding syndrome. Varying amounts of electrolytes are lost from the different gastro-intestinal secretions. Table 7.10 gives an indication of the content of various gastro-intestinal secretions. This should be taken into account when formulating PN for a patient who may have such losses.

Administration of PN

Routes of administration

PN can be administered peripherally or centrally.

Peripheral route

Administration of PN via a peripheral venous catheter should be considered for patients who are likely to need short-term feeding (less than 14 days) and who have no other need for central venous access. Peripheral lines are less costly than central lines and they may be inserted at the bedside providing the patient has good venous access. Ultrasound machines may be used to aid placement. There is no need for a chest X-ray to confirm placement as the line does not reach the central circulation. Mid-lines should be considered which are usually about 20 cm long.

Care should be taken when formulating PN to be administered via a peripheral catheter with regard to the tonicity of the solution.

Some indications and contraindications to the use of the peripheral route are summarised in Box 7.3.

Peripheral administration is sometimes complicated or delayed by phlebitis, where an insult to the endothelial vessel wall causes inflammation, redness, pain and possible extravasation. Hot and cold compresses have been used to treat this. A 5 mg glyceryl trinitrate patch placed where the line tip is estimated to be may cause some local vasodilation which is believed to prevent thrombophlebitis (Khawaja and Williams, 1991). Peripheral tolerance can be influenced by a range of factors (Box 7.4).

Many consider that the tonicity of the infused solution or emulsion is a key factor defining peripheral infusion tolerance. The total number of osmotically active particles in the intracellular and extracellular fluids is essentially the same, approximately 290–310 mOsmol/L. When a lipid emulsion is included, infusions of approximately three times this osmolarity are generally well tolerated via the peripheral route and there are reports of success with higher levels. However, other factors should also be considered. Patient factors, such as vein

Box 7.3 Indications and contraindications to the use of peripheral parenteral nutrition

Indications
- Duration of feed likely to be short term
- Supplemental feeding
- Compromised access to central circulation, for example, local trauma, surgery or thrombosis
- No immediate facilities or trained staff to insert central catheter
- High risk of fungal or bacterial sepsis, for example, patients with purulent tracheostomy secretions, immune deficiency state, history of repeated sepsis
- Contraindication to central venous catheterisation

Contraindications
- Inadequate or inaccessible peripheral veins
- Large volumes of administration
- High calorie/nitrogen requirements alongside fluid restrictions (admixture osmolarity too high)

Box 7.4 Factors that improve tolerance to peripheral lines

- Aseptic insertion and line care
- Selection of large vessel with good blood flow and direct path, for example, cephalic vein
- Fine-bore catheter (22G) for minimal trauma on insertion and disturbance of blood flow
- Fine polyurethane catheter
- Secure catheter to minimise physical trauma
- Glyceryl trinitrate patch distal to insertion site, over tip to vasodilate vein
- Flushing of lines not in use
- Low-tonicity infusions
- Inclusion of lipid emulsion; venoprotective and isotonic with blood

fragility and blood flow, may mean that some infusion episodes are better tolerated than others. The osmolarity of a PN formulation can be estimated by applying the following equation:

$$= \frac{\sum[\text{osmolarity}_n(\text{mOsmol/L}) \times \text{volume}_n(\text{L})]}{\text{Total volume(L)}},$$

where *n* indicates the component.

By considering the macronutrients included in the regimen, that is, the amino acids, glucose and lipid, an estimation of the osmolarity can be made. The value will be increased by electrolyte or micronutrient additions; however, since the peripheral tolerance is affected by so many factors, including tonicity, and because the limit is only an estimate, the effect of these additions is relatively low unless high levels of monovalent ions are included.

Central route

The central venous route is indicated when longer-term feeding is anticipated, high tonicity or large volume formulations are required, or the peripheral route is inaccessible. The rapid and turbulent blood flow in the central circulation and the constant movement of the heart ensure rapid mixing and reduce the risk of osmotically induced injury to the endothelium.

A range of single-, double-, triple- and quadruple-lumen central lines are available and one lumen must be dedicated for the intravenous nutrition. These lines require skilful insertion, usually into the jugular or subclavian vein, and confirmation of their position by X-ray. This relatively invasive and costly procedure is performed by trained medical staff. Tunnelling of the line to an appropriate exit site facilitates line care and may reduce the incidence of significant line sepsis. The femoral route is not favoured due to a higher incidence of sepsis. If cared for well, a tunnelled central line placed in a patient receiving home PN may last for many years.

Peripherally Inserted Central Catheters (PICCs)

PICCs are typically inserted into a peripheral vein, usually the cephalic or basilic in the upper arm, with the exit tip in the superior vena cava just above the right atrium. As the name suggests, they are used for the central administration of infusions. Single- and double-lumen versions are available; some also have a one-way valve to prevent backflow. Insertion is less invasive than for conventional central lines and can be undertaken by trained nurse practitioners at the bedside. A chest X-ray is necessary to confirm placement.

Infusion control

Pumps

PN must always be administered under the control of an infusion pump. Acute overload of fluid, nutrition and electrolytes can have morbid consequences.

Infusion pumps should be used with an appropriate infusion or giving set which is compatible with both the infusion pump and the PN admixture. For home patients, small, simple battery-powered ambulatory pumps are favoured.

Temperature

PN should be at room temperature when it is infused. It must, therefore, be removed from the refrigerator in which it is stored approximately 2 h before connection. No external heat should be applied, although intermittent inversion of the bag may help.

If a cold admixture is infused, the patient may experience infusion discomfort, and the acute release of gas from where it was dissolved in the admixture may cause the pump to alarm 'air in line'.

Compounded formulations

Historically, PN was administered from a series of separate bottles, where health care staff had to accurately and safely manage a combination of giving sets, infusion rates and total infusion times. Most patients now receive their complete nutrition from a single daily bag of a pharmaceutically stable PN formulation.

Various terms are used to describe the PN formulation, depending on whether lipid is included. If it contains lipid, it is called a 3-in-1, ternary or all-in-one admixture, if no lipid is present, the terms 2-in-1, binary or aqueous admixture are used. Various methods now exist for compounding PN, these range from high-tech, computer run compounding machines through to basic principle techniques such as gravity filling.

Standardised formulations

Depending on the type (size and specialty) of the hospital, a range of standard formulations are maintained and supported with prescribing guidelines. These may be compounded from scratch, compounded from 'base-bags' locally or by a licensed unit, or purchased as licensed ready-to-use presentations.

The range is specifically selected to meet the needs of the patients managed by the hospital and will typically include a

low-tonicity regimen suitable for peripheral administration, a higher calorie and nitrogen regimen for central administration to catabolic patients and a high-tonicity regimen for fluid-restricted patients. Baseline electrolytes will generally be included, although the flexibility for reduced levels is usually offered.

Licensed ready-to-use products

A range of licensed ready-to-use preparations are available and should have micronutrients added prior to infusing. For convenience, baseline electrolyte levels are included in many formulations and meet the needs of most patients and additional electrolytes may be added up to the limits set by the manufacturer. Electrolyte-free options are also available. Some are licensed for use in paediatrics and/or for peripheral use. Manufacturers advise on stability and shelf-life for electrolyte and micronutrient additions. The range of ready-to-use products includes:

- triple chamber bags (OliClinomel®, Kabiven®, StructoKabiven® and Nutriflex® Lipid ranges): chambers separately pre-filled with lipid, amino acid and glucose and terminally sterilised, these are activated by applying external pressure so weak seal peels open, mixing the contents to form a 3-in-1 formulation.
- dual chamber bags (Clinimix® and Nutriflex® ranges): chambers separately pre-filled with amino acid and glucose and terminally sterilised, these are activated to form a 2-in-1 formulation. They provide the flexibility to allow staff to omit or add a compatible lipid.

The range of commercially available PN formulations is continually expanding. For hospital pharmacies who do not have compounding facilities, this offers an opportunity to ensure the correct formulation is given to meet individual patients needs. PN formulations are now available with micronutrients added and with extended shelf-lives when stored in a refrigerator.

Cyclic infusions

Cyclic PN is when the daily requirements are administered over a short period. A classic example is the stable home patient who administers their feed overnight, freeing themselves from the constraints of an infusion during the day. This enables them to have more physical freedom and improves their quality of life. Some patients, however, prefer to administer their PN during the day time. This is made possible by use of a small ambulatory pump and a back pack in which they may carry their PN.

Since cyclic feeding more closely simulates the human feeding pattern and is a closer match to normal hormonal and metabolic cycles, it also offers a range of metabolic and clinical advantages. Steatosis, fatty infiltration of the liver, is less common and may be corrected by employing cyclic feeding because the feed-free period facilitates lipolysis and fat mobilisation. Peripheral tolerance may be improved as the endothelia recover between infusion periods.

Initially, the patient should receive the PN infusion slowly over the full 24 h, as tolerated, the rate of infusion can be increased slowly to decrease the infusion time. This should be done over a series of days. During this period, the patient must be monitored closely for any signs of fluid, electrolyte or acid-base imbalance and hyper/hypoglycaemia. For example, on stopping the infusion, rebound hypoglycaemia may occur.

Pharmaceutical issues

Having identified the balance of nutrients required for a patient in a single day, it is necessary to formulate a physically and chemically stable aseptically prepared admixture. PN admixtures contain over 50 chemical entities and, as such, are extremely complex and have many chemical interactions taking place which could lead to instability in the final formulation. Professional advice or appropriate reference material should

Table 7.10 Electrolyte content of gastro-intestinal secretions

Intestinal tract locality	Volume (ml)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
Saliva	1500	10	25	10	30
Gastric juice (fasting)	1500	60	15	90	15
Pancreatic fistula	700	140	5	75	120
Biliary fistula	500	145	5	100	40
Jejunostomy	2000–3000	110	5	100	30
Ileostomy	500	115	8	45	30
Proximal colostomy	300	80	20	45	30
Diarrhoea	500–1500	120	25	90	45

be sought and used before compounding and administering of PN takes place. Manufacturers and third party experts can advise on stability issues.

Physical stability

Physical instability takes a number of forms including precipitation of crystalline material and breakdown of the lipid emulsion.

Precipitation

Precipitation carries two key risks. First, the potential to infuse solid particles to the narrow pulmonary capillaries may result in fatal emboli. Second, the prescribed nutrients may not be infused to the patient. Clinically dangerous precipitates may not always be visible to the naked eye, especially if lipid emulsion is present. They may also develop over time, and an apparently 'safe' admixture may develop fatal precipitates when in use.

Precipitation of solid is epitomised by the formation of calcium phosphate; this is of special concern in neonatal admixtures where the requirements to prevent hypophosphataemic rickets and severe osteopenia may exceed the safe concentrations. Such concentrations are rarely seen in adult regimens. It is known that calcium and phosphate can form a number of different salt forms each with different solubility profiles, for example, $Ca(H_2PO_4)_2$ which is highly soluble in comparison to $CaHPO_4$ and $Ca_3(PO_4)_2$. $Ca_3(PO_4)_2$ precipitation occurs relatively immediate and has a white, fluffy amorphous appearance; however, $CaHPO_4.2H_2O$ precipitation is time mediated and has a more crystalline appearance.

Factors affecting calcium phosphate precipitation are shown in Table 7.11. Practical measures can be taken to minimise the risks; these include accurate calculation of the proposed formulation, comparison against professionally defined comprehensive matrices and thorough mixing. Solubility curves and algorithms should be used with extreme caution, even if they are quoted for a specific amino acid source, this is because they do not consider all the factors and do not consistently identify risk. Assuming the sodium content can be tolerated, use of an organic phosphate salt form may be beneficial due to the higher solubility of the sodium glycerophosphate salt form.

Trace elements have also been associated with clinically significant precipitation; these include iron phosphate and copper sulphide (hydrogen sulphide from the minor degradation of cysteine/cystine). These very fine precipitate forms are less likely to cause occlusion of catheters or lung capillaries, but have been associated with significant clinical delivery losses when they are taken up by inline filtration devices.

Table 7.11 Factors affecting calcium phosphate precipitation

Factor	Mechanism and effect
pH	Low pH supports solubility, whereas a higher pH supports precipitation. Depending on the amount and buffering capacity of the amino acids, this can be affected by different concentrations and sources of glucose solution and acetate salt forms.
Temperature	Higher temperatures associated with greater precipitation, increased availability of free calcium to interact and a shift to the more insoluble salt forms.
Amino acids	Buffer pH changes. Complex with calcium so less available to react with phosphate. Both the source of amino acid and the relative content are important.
Magnesium	Complex with phosphate forming soluble salts rather than less soluble calcium salts.
Calcium salt form	Calcium chloride dissociates more readily than calcium gluconate, releasing it to react with the phosphate.
Phosphate salt form	Monobasic salts, for example, dipotassium phosphate, dissociate more readily than dibasic salts, for example, potassium acid phosphate, releasing phosphate to react with the calcium. Organic salts, such as sodium glycerophosphate and glucose-1-phosphate, are more stable.
Mixing order	Optimum stability achieved by only permitting calcium and phosphate to come together in a large volume admixture. Agitate between additions to avoid pockets of concentration.

Lipid destabilisation

The oil-in-water lipid emulsions are sensitive to destabilisation by a range of factors including the presence of positively charged ions, pH changes and changes in environmental temperature. The lipid globules may come together and coalesce to form larger globules and release free oil; this could occlude the lung microvasculature and cause respiratory and circulatory compromise and lead to death.

Positively charged ions destabilise the admixture by drawing the negatively charged lipid globules together, overwhelming the electromechanical repulsion of the charged phospholipids and increasing their tendency to join or coalesce. Divalent and trivalent ions have a more significant effect; therefore, there are tightly defined limits for the amount of Ca^{2+}, Mg^{2+} and Fe^{3+} that can be added to a 3-in-1 admixture. Although the limits for the other polyvalent ions (such as zinc and selenium) are also controlled, because they are given in micromolar or nanomolar quantities, they are less of a problem. Low concentrations of amino acids and extremes of glucose

concentration (high and low) also reduce the stability of the emulsion and increase the tendency for creaming and cracking of the lipid emulsion.

The naked eye can identify large-scale destabilisation, as shown in Table 7.12; however, the limitations of this method need to be recognised; clinically significant destabilisation might not be visible to the naked eye. In practice, stability laboratories use specialised technical equipment to determine defined criteria so as to establish the physical stability of a formulation. These tests include assessing changes in lipid globule size distribution with optical microscopes, and variety of particle size analysis instruments against the defined limits of pharmaceutical acceptance. A wide safety margin is applied.

Chemical stability

Chemical stability takes many forms, notably chemical degradation of the vitamins and amino acids.

Vitamin stability

Many vitamins readily undergo chemical degradation, and vitamin stability often defines the shelf-life of a given formulation.

Vitamin C (ascorbic acid), the least stable component, is generally regarded as the marker for vitamin degradation. Vitamin C oxidation is accelerated by heat, oxygen and certain trace elements, including copper. Other examples include vitamin A photolysis and vitamin E photo-oxidation. Measures that minimise oxygen presence, such as minimal aeration during compounding, evacuation of air at the end of compounding and use of multi-laminated oxygen barrier bags, and light protection of admixture containers and delivery sets are recommended.

Amino acid stability

The amino acid profile should be maintained for the shelf-life of the formulation and manufacturers perform assays to confirm this prior to issuing stability reports.

Maillard reaction

The Maillard reaction is a complex pathway of chemical reactions that starts with a condensation of the carbonyl group of the glucose and the amino group of the amino acid. At present, relatively little is known about the clinical effects of these Maillard reaction products; however, it is prudent to minimise their presence by protecting from light and avoiding high temperatures.

Microbial contamination

PN is a highly nutritious medium whose hypertonicity will partially limit microbial growth potential. Growth in the presence of lipid emulsion is greater. Pharmaceutical developments have enabled terminal sterilisation of many of the components, including the multi-chamber bag presentations; however, additional manipulations should only be performed using validated aseptic techniques in appropriate pharmaceutically clean environments by suitably trained staff. Nurses, patients and carers must be trained to apply aseptic methods when connecting and disconnecting infusions, for this reason, many centres have documented line care and PN protocols.

Shelf-life and temperature control

The manufacturer may be able to provide physical and chemical stability data to support a formulation for a shelf-life of up to 90 days at 2–8°C followed by 24 h at room temperature for infusion; this assumes that a strict aseptic technique is used during compounding. Units holding a manufacturing license covering aseptic compounding of PN are potentially able to assign this full shelf-life (if stability data is available), whilst unlicensed units are limited to a maximum shelf-life of 7 days.

PN must be stored and transported within the defined temperature limits and should not be exposed to temperature cycling (e.g. the formulations must not freeze); for this reason, a validated cold-chain must be employed especially when delivering formulations to home care patients. Pharmaceutical-grade fridges should be used and monitored

Table 7.12 Lipid instability

	Description	Visual observation
Stable, normal emulsion	Lipid globules equally dispersed. Suitable for administration	Normal emulsion
Light creaming	Lipid globules rising to the top of the bag. Slight layering visible. Readily redisperses on inverting the bag. Suitable for administration	Light creaming
Heavy creaming, flocculation	Lipid globules coming together but not joining. Rising to the top of the bag. More obvious layering visible. Readily redisperses on inverting the bag. Acceptable for administration	Heavy creaming
Coalescence	Lipid globules come together, coalesce to form larger globules and rise to the surface. Larger globules join, releasing free oil. Irreversible destabilisation of the lipid emulsion. Not suitable for administration	Cracked. Oil layer viewed close up

to ensure appropriate air cycling and temperature maintenance. The temperature during the infusion period should be known with neonatal units and their patient incubators classically maintained at higher temperatures; therefore, formulations used for this environment must have been stability-validated at these temperatures.

Drug stability

The addition of drugs to PN admixtures, or Y-site co-administration, is actively discouraged unless the compatibility has been formally confirmed. Wherever possible, the PN should be administered through a dedicated line. Multilumen catheters can be used to infuse PN separately from other infusion(s); however, extreme competition for intravenous access may prompt consideration of drug and PN combinations. Many factors need to be considered: the physical and chemical stability of the PN, the physical and chemical stability of the drug, the bioavailability of the drug (especially when a lipid emulsion is present) and the effect of stopping and starting Y-site infusions on the actual administration rates. It is not possible to reliably extrapolate data from a specific PN composition, between brands of solutions and salt forms or between brands or doses of drugs. A range of studies has been performed and published; however, these should be used with caution.

In practice, drugs should only be infused with PN when all other possibilities have been exhausted. These may include gaining further intravenous access and changing the drug(s) to clinically acceptable non-intravenous alternatives. The relative risks of stopping and starting the PN infusion and repeatedly breaking the infusion circuit should be fully considered before sharing a line for separate infusions of PN and drug. In most cases, the risks outweigh the benefits; however, if this option is adopted, the line must be flushed before and after with an appropriate volume of solution known to be stable with both the PN and the drug. Strict aseptic technique should be adopted to minimise the risk of contaminating the line and infusions.

Filtration

All intravenous fluids pass through the delicate lung microvasculature with its capillary diameter of 8–12 µm. The presence of particulate matter has been demonstrated to cause direct embolisation, direct damage to the endothelia, formation of granulomata and formation of foreign body giant cells, and to have a thrombogenic effect. In addition, the presence of microbial and fungal matter can cause a serious infection or inflammatory response.

Precautions taken to minimise the particulate load of the compounded admixture must include:

- use of filter needles or straws (5 µm) during compounding to catch larger particles such as cored rubber from bottles and glass shards from ampoules
- air particle levels kept within defined limits in aseptic rooms by the use of air filters and non-shedding clothing and wipes
- use of quality raw materials with minimal particulate presence, including empty bags and leads
- confirmation of physical and chemical stability of the formulation prior to aseptic compounding applying approved mixing order (stability for the required shelf-life time and conditions)

Guidelines have been published that endorse the use of filters, especially for patients requiring intensive or prolonged parenteral therapy, including home patients, the immunocompromised, neonates and children (Bethune et al., 2001). The filter should be placed as close to the patient as possible and validated for the PN to be used. For 2-in-1 formulations, 0.2 µm filters may be used, for 3-in-1 formulations, validated 1.2 µm filters may be used.

Light protection

It is widely recognised that exposure to light, notably phototherapy light and intense sunlight, may increase the degradation rate of certain constituents such as vitamins A and E. It is recommended that all regimens should be protected from light both during storage and during infusion, since

- the presence of a lipid emulsion does not totally protect against vitamin photodegradation
- the Maillard reaction is influenced by light exposure
- ongoing research suggests lipid peroxidation is accelerated by a range of factors, including exposure to certain wavelengths of light
- validated bag and delivery set covers should only be used

Nutritional assessment and monitoring

Initial assessment

Once screening has identified that a patient is in need of nutritional intervention, a more detailed assessment is performed; this will include an evaluation of nutritional requirements, the expected course of the underlying disease, consideration of the enteral route and, where appropriate, identification of access routes for PN. This will be supported by a clinical assessment that will include:

- clinical history
- dietary history
- physical examination
- anthropometry including muscle function tests
- biochemical, haematological and immunological review.

Monitoring

PN monitoring has a number of objectives. It should

- evaluate ongoing nutritional requirements, including fluid and electrolytes
- determine the effectiveness of the nutritional intervention

- facilitate early recognition of complications
- identify any deficiency, overload or toxicity to individual nutrients
- determine discrepancies between prescribed, delivered and received dose.

Regular monitoring contributes to the success of the PN and a monitoring protocol should be in place for each individual patient. Baseline data should be recorded so deviations can be recognised and interpreted. In the early stages, while the patient is in the acute stage of their illness and the nutritional requirements are being established, the frequency of monitoring will be greatest. Some tests may be defined by the underlying disease state, rather than by the presence of PN *per se*. As the patient's status stabilises, the frequency of monitoring will reduce, although the range of parameters monitored is likely to increase. Examples of parameters monitored include the following:

- *Clinical symptoms or presentation:* may be specific, for example, thrombophlebitis, or non-specific, for example, confusion.
- *Temperature, blood pressure and pulse:* vigilance for the risk of sepsis.
- *Fluid balance and weight:* acute weight changes reflect fluid gain or loss and prompt review of the volume of the PN. Slow, progressive changes are more likely to reflect nutritional status.
- *Nitrogen balance:* an assessment of urine urea and insensible loss and their relation to nitrogen input. It is difficult to obtain accurate figures.
- *Visceral proteins*: albumin levels may indicate malnutrition but its long half-life limits sensitivity to detect acute changes in nutritional status. Other markers with a shorter half-life may be more useful, for example, transferrin.
- *Haematology:* platelet counts and clotting studies for thrombocytopenia.
- *C-reactive protein:* monitor the inflammatory process.
- *Blood glucose:* hyperglycaemia is a relatively frequent complication. Management includes either a reduction in the infused dose or lengthening of the infusion period. If these measures fail, insulin may be used. Hyperglycaemia may also indicate sepsis. Rebound hypoglycaemia can occur when an infusion is stopped. If this is a problem, the infusion should be tapered off during the last hour or two of the infusion. Some infusion pumps are programmed to do this automatically.
- *Lipid tolerance:* turbidity, cholesterol and triglyceride profiles required.
- *Electrolyte profile:* indicates appropriate provision or complicating clinical disorder. In the first few days, low potassium, magnesium and/or phosphate with or without clinical symptoms may reflect the refeeding syndrome (see below).
- *Liver function tests:* an abnormal liver profile may be observed and it is often difficult to identify a single cause. PN and other factors such as sepsis, drug therapy and underlying disease may all interplay. In adults, PN-induced abnormalities tend to be mild, reversible and self-limiting. In the early stages, fatty liver (steatosis) is seen. In longer-term patients, a cholestatic picture tends to present. Varying the type of lipid used and removing lipid from some formulations may be of benefit.
- *Anthropometry:* assesses longer-term status.
- *Acid–base profile:* indicative of respiratory or metabolic compromise and may require review of PN formulation.
- *Vitamin and trace element screen:* a range of single compounds or markers to consider tolerance and identify deficiencies, although of limited value as some tests are non-specific and inaccurate.
- *Catheter entry site:* vigilance for phlebitis, erythema, extravasation, infection, misplacement.

Complications

Complications of PN fall into two main categories: catheter-related and metabolic (Box 7.5). Overall, the incidence of such complications has reduced because of increased knowledge and skills together with more successful management (Maroulis and Kalfarentzos, 2000).

Line sepsis

This is a serious and potentially life-threatening condition. Monitoring protocols should ensure that signs of infection are identified early and a local decision pathway should be in place to guide efficient diagnosis and management. Management will depend upon the type of line and the source of infection. Alternative sources of sepsis should be considered. Initially, the PN is usually stopped.

Box 7.5 Examples of complications during parenteral nutrition

Catheter-related
- Thrombophlebitis (peripheral)
- Catheter-related infection, local or systemic
- Venous thrombosis
- Line occlusion (lipid, thrombus, particulate, mechanical)
- Pneumothorax, catheter malposition, vessel laceration, embolism, hydrothorax, dysrhythmias, incorrect placement (central)

Metabolic
- Hyperglycaemia or hypoglycaemia
- Electrolyte imbalance
- Lipid intolerance
- Refeeding syndrome
- Dehydration or fluid overload
- Specific nutritional deficiency or overload
- Liver disease or biliary disease
- Gastro-intestinal atrophy
- Metabolic bone dysfunction (in long term)
- Thrombocytopenia
- Adverse events with parenteral nutrition components
- Essential fatty acid deficiency

Line occlusion

Line occlusion may be caused by a number of factors, including:

- fibrin sheath forming around the line, or a thrombosis blocking the tip
- internal blockage of lipid, blood clot or salt and drug precipitates
- line kinking
- particulate blockage of a protective line filter.

Management will depend on the cause of the occlusion; in general, the aim is to save the line and resume feeding with minimum risk for the patient. The use of locks and flushes with alteplase (for fibrin and thrombosis), ethanol (for lipid deposits) and dilute hydrochloric acid (for salt and drug precipitates) may be considered. In some cases, the lines may need to be replaced.

These complications can be minimised by having a dedicated line for PN, flushing the line well with sodium chloride 0.9% before and after use and a regular slow flush of ethanol 20% may be used to prevent lipid deposition.

Refeeding syndrome

Patients should be assessed as to their risk of developing refeeding syndrome (see Table 7.13). Refeeding syndrome can be defined as 'the potentially fatal shifts in fluids and electrolytes that may occur in malnourished patients receiving nutrition'. Undernourished patients are catabolic and their major sources of energy are fat and muscle. As the PN infusion (which contains glucose) starts, this catabolic state is pushed to anabolic which in turn causes a surge of insulin. As the insulin levels increase, there is an intracellular shift of magnesium, potassium and phosphate, and acute hypomanganesaemia, hypokalaemia and hypophosphataemia result. This can cause cardiac and neurological dysfunction and may be fatal. PN should be gradually increased over a period of 2–7 days depending on the patient's body mass index and risk of developing refeeding syndrome. Oral thiamine and vitamin B compound strong or full dose intravenous vitamin B preparation may be administered before PN is started and for the first few days of infusion.

Table 7.13 Risk factors for developing refeeding syndrome (NICE, 2006)

One or more of the following:	Two or more of the following:
BMI <16 kg/m^2	BMI <18.5 kg/m^2
Unintentional weight loss greater than 15% within the last 3–6 months	Unintentional weight loss greater than 10% within the last 3–6 months
Little or no nutritional intake for more than 10 days	Little or no nutritional intake for more than 5 days
Low levels of potassium, phosphate or magnesium prior to feeding	A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics

Specific disease states

Liver

Although abnormal liver function tests associated with short-term PN are usually benign and transient, liver dysfunction in long-term PN patients is one of the most prevalent and severe complications. Its underlying pathophysiology, however, largely remains to be elucidated. The content of PN should be examined and care should be taken not to overfeed with glucose and/or lipid. Supplementation with taurine in the formulation has been reported to ameliorate PN associated cholestasis through promoted bile flow. Various lipid preparations are now available, including preparations containing fish oils which have been reported to be beneficial in reversing liver disease (De Meijer et al., 2009). Lipid emulsions containing a mix of medium and long chain triglycerides are also available and have an improved liver tolerability. Due to the complexity of liver function, the range of potential disorders and its role in metabolism, the use of PN in liver disease is not without problems. Consensus guidelines for the use of PN in liver disease have been published (Plauth et al., 2009). Nutritional intervention may be essential for recovery, although care must be exercised with amino acid input and the risk of encephalopathy, calorie input and metabolic capacity, and the reduced clearance of trace elements such as copper and manganese (Maroulis and Kalfarentzos, 2000). Low-sodium, low-volume feeds are indicated if there is ascites. Cyclic feeding appears useful, especially in steatosis.

Renal failure

Fluid and electrolyte balance demand close attention, and guidelines for nutrition in adult renal failure are available (Cano et al., 2009). A low volume and poor quality urine output may necessitate a concentrated PN formulation with a reduction in electrolyte content, particularly a reduction in potassium and phosphate. In the polyuric phase or the nephrotic syndrome, a higher volume formulation may be required. If there is fluid retention, ideal body weight should be used for calculating requirements rather than the actual body weight.

The metabolic stress of acute renal failure and the malnutrition of chronic renal failure may initially demand relatively high nutritional requirements; however, nitrogen restriction may be necessary to control uraemia in the absence of dialysis or filtration and to avoid uraemia-related impaired glucose tolerance, because of peripheral insulin resistance, and lipid clearance.

Micronutrient requirements may also change in renal disease. For example, renal clearance of zinc, selenium, fluoride and chromium is reduced and there is less renal 1α-hydroxylation of vitamin D.

Intradialytic PN (IDPN) may be administered at the same time as dialysis; however, this is not without complications. High blood sugars and fluid overload can be a problem and there is uncertainty as to how much of the PN is

retained by the body and how much is removed by dialysis. Administration requires local guidelines and monitoring to be in place (Foulks, 1999; Lazarus, 1999).

Pancreatitis

Acute pancreatitis is a metabolic stress that requires high-level nutritional support and pancreatic rest to recover. Guidelines for nutrition in acute pancreatitis are available (Gianotti et al., 2009). While enteral nutrition stimulates the pancreas, PN does not appear to. Hyperglycaemia may occur and require exogenous insulin.

Sepsis and injury

Significant fluctuations in macronutrient metabolism are seen during sepsis and injury. There are two metabolic phases: the 'ebb' phase of 24–48 h and the following 'flow' phase. The initial hyperglycaemia, reflecting a reduced utilisation of glucose, is followed by a longer catabolic state with increased utilisation of lipid and amino acids. The effect of the different lipid emulsions on immune function is the subject of much research. It is important not to overfeed and also to consider the reduced glucose tolerance during the critical days. This is due to increased insulin resistance and incomplete glucose oxidation. Exogenous insulin may be required.

Respiratory

While underfeeding and malnutrition can compromise respiratory effort and muscle function, overfeeding can equally compromise respiratory function due to increased carbon dioxide and lipid effects on the circulation. While chronic respiratory disease may be linked with a long-standing malnutrition, the patient with acute disease will generally be hypermetabolic.

Cardiac failure

Cardiac failure and multiple drug therapy may limit the volume of PN that can be infused. Concentrated formulations are used and, as a consequence of the high tonicity, administered via the central route. Close electrolyte monitoring and adjustment is required. Cardiac drugs may affect electrolyte clearance. Although central lines may already be in use for other drugs or cardiac monitoring, it is essential to maintain a dedicated lumen or line for the feed.

Diabetes mellitus

Diabetic patients can generally be maintained with standard dual-energy regimens. It is important to use insulin to manage blood glucose rather than reduce the nutritional provision of the feed. Close glucose monitoring will guide exogenous insulin administration. This should be given as a separate infusion (sliding scale) or, if the patient is stable, in bolus doses. Insulin should not be included within the PN formulation due to stability problems and variable adsorption to the equipment. Y-site infusion with the PN should be avoided as changes in insulin rates will be delayed and changes in feed rates will result in significant fluctuations in insulin administration. Extra potassium and phosphate may be required due to the impact of the glucose and insulin. Long-term PN patients may need differing insulin regimes depending on the glucose load (aqueous/lipid) in the formulation. Although using oral antihypoglycaemic agents with PN may be considered, care should be taken as to the potentially erratic absorption and so varying blood glucose levels.

Cancer and palliative care

Nutritional support in cancer and palliative care is guided by the potential risks and benefits of the intervention, alongside the wishes of the patient and their carers. Further research is required to evaluate the effects of PN on length and quality of life.

Standard PN may be useful during prolonged periods of gastro-intestinal toxicity, as in bone marrow transplant patients. The use of PN is not thought to stimulate tumour growth (Nitenberg and Raynard, 2000).

Short bowel syndrome

The small intestine is defined as 'short' if it is less than 100 cm. Treatment options depend upon which part of the gut has been removed and the functional state of the remaining organ. The surface area for absorption of nutrition and reabsorption of fluid and electrolytes is significantly compromised. Fluid and electrolyte balance needs to be managed closely due to the high-volume losses. High-volume PN formulations with raised electrolyte content (notably sodium and magnesium) may be required. Vitamin and trace element provision is very important.

Long-term PN

Home care is well established in the UK, with some patients successfully supported for over 20 years. Total or supplemental PN may be appropriate. Trace elements, notably selenium, should be managed closely as requirements may be increased.

Most patients are extremely well informed about their underlying disease and their PN; many also benefit from support group PINNT (Patients on Intravenous and Nasogastric Nutrition Therapy) and LITRE (Looking into the Requirements for Equipment), a standing committee of BAPEN which looks at equipment issues.

There are an increasing number of patients at home on PN. Scotland and Wales now have designated networks to care for these patients. Many patients are trained to connect and disconnect their PN and to care for their central lines. Patients are encouraged to lead as active and normal life as possible. Foreign travel is now possible for patients on home PN, as are most other normal daily activities and sports (Staun et al., 2009).

Paediatric PN

Nutritional requirements

Early nutritional intervention is required in paediatric patients due to their low reserve, especially in neonates. Where possible, premature neonates should commence feeding from day 1. In addition to requirements for the maintenance of body tissue, function and repair, it is also important to support growth and development, especially in the infant and adolescent.

Typical guidelines for average daily requirements of fluid, energy and nitrogen are shown in Table 7.14. The dual-energy approach is favoured in paediatrics. Approximately 30% of the non-protein calories are provided as lipid using a 20% emulsion. Most centres gradually increase the lipid provision from day 1 from 1 g/kg/day to 2 g/kg/day and then 3 g/kg/day, monitoring lipid clearance through the serum triglyceride level. This ensures the essential fatty acid requirements of premature neonates are met.

Formulation and stability issues

Many centres use standard PN formulations including the specific paediatric amino acid solutions (Primene® or Vaminolact®). Prescriptions and formulations are tailored to reflect clinical status, biochemistry and nutritional requirements.

Micronutrients are included daily. Paediatric licensed preparations are available and are included on a ml/kg basis up to a maximum total volume (Peditrace®, Solivito® N and Vitlipid® N Infant). Electrolytes are also monitored and included in all formulations on a mmol/kg basis. Acid–base balance should be considered. Potassium and sodium acetate salt forms are used in balance with the chloride salt forms in neonatal formulae to avoid excessive chloride

Table 7.14 Suggested paediatric daily PN requirements (adapted from Koletzko et al., 2005)

		Day 1	Day 2	Day 3	Day 4	Na^+	K^+	Ca^{2+}	Mg^{2+}
		>1 month but <10 kg				mmol/kg/day			
Fluid requirement	100 ml/kg								
						3	2.5	0.6	0.1
Nitrogen	g/kg	0.15	0.2	0.3	0.4				
Glucose	g/kg	10	12	14	16				
Lipid	g/kg	1	2	2	3				
Phosphate[a]	mmol/kg/day	0.5	0.58	0.58	0.6				
		10–15 kg							
Fluid requirement	1000 ml + 50 ml/kg for each kg above 10 kg								
						3	2.5	0.2	0.07
Nitrogen	g/kg	0.15	0.2	0.3	0.3				
Glucose	g/kg	6	8	10	12				
Lipid	g/kg	1.5	2	2.5	2.5				
Phosphate[a]	mmol/kg/day	0.23	0.27	0.3	0.3				
		16–20 kg							
Fluid requirement	1000 ml + 50 ml/kg for each kg above 10 kg								
						3	2	0.2	0.07
Nitrogen	g/kg	0.15	0.2	0.3	0.3				
Glucose	g/kg	4	6	8	10				
Lipid	g/kg	1.5	2	2	2				
Phosphate[a]	mmol/kg/day	0.22	0.26	0.26	0.26				

Continued

Table 7.14 Suggested paediatric daily PN requirements (adapted from Koletzko et al., 2005)—Cont'd

21–30 kg								
Fluid requirement	1500 ml + 20 ml/kg for each kg above 20 kg							
					3	2	0.2	0.07
Nitrogen	g/kg	0.2	0.3	0.3				
Glucose	g/kg	4	6	8				
Lipid	g/kg	1	2	2				
Phosphate[a]	mmol/kg/day	0.18	0.26	0.26				
>30 kg								
Fluid requirement	1500 ml + 20 ml/kg for each kg above 20 kg							
					3	2	0.2	0.07
Nitrogen	g/kg	0.15	0.2					
Glucose	g/kg	3	5					
Lipid	g/kg	1	2					
Phosphate[a]	mmol/kg/day	0.18	0.25					

[a]includes phosphate from lipid emulsion and Vitlipid® preparations.

input contributing to acidosis (acetate is metabolised to bicarbonate, an alkali). In the initial stages, neonates tend to hypernatraemia due to relatively poor renal clearance; this should be reflected in the standard formulae used.

Due to the balance of nutritional requirements, a relatively high glucose requirement with high calcium and phosphate provision, the neonatal and paediatric prescription may be supplied by a separate 2-in-1 bag of amino acids, glucose, trace elements and electrolytes and a lipid syringe with vitamins. These are generally given concurrently, joining at a Y-site. Older children can sometimes be managed with 3-in-1 formulations. A single infusion is particularly useful in the home care environment. Some ready-to-use formulations are licensed for use in paediatrics and include the Kabiven® and OliClinomel® range.

Improved stability profiles with the new lipid emulsions, and increasing stability data, may support 3-in-1 formulations that meet the nutritional requirements of younger children.

Concerns over the contamination of calcium gluconate with aluminium and the association between aluminium contamination of neonatal PN and impaired neurological development have favoured the use of calcium chloride over gluconate; however, chloride load should be considered if the former is used. If calcum gluconate is to be used it must be from plastic containers.

Heparin

Historically, low concentrations of heparin were included in 2-in-1 formulations in an attempt to improve fat clearance through enhanced triglyceride hydrolysis, prevent the formation of fibrin around the infusion line, reduce thrombosis and reduce thrombophlebitis during peripheral infusion; however, this is no longer recommended. It is recognised that when the 2-in-1 formulation comes into contact with the lipid phase, calcium-heparin bridges form between these lipid globules, destabilising the formulation. Also, there is limited evidence of clinical benefit of the heparin inclusion.

Route of administration

Peripheral administration is less common in neonates and children due to the risk of thrombophlebitis; however, it is useful when low-concentration, short-term PN is required and there is good peripheral access. The maximum glucose concentration for peripheral administration in paediatrics is generally regarded to be 12%. However, considering all the other factors that can affect the tonicity of a regimen and peripheral tolerance, it is clear that this is a relatively simplistic perspective. Many centres favour a limit of 10% with close clinical observation.

Central administration is via a PICC, a long-term tunnelled central line, a jugular or subclavian line. Femoral lines are a less preferred option owing to their location and, therefore, high risk of becoming infected.

Case study

Case 7.1

Mrs B, aged 47, was admitted for investigation of chronic diarrhoea and 6 kg weight loss over the past 3 months.

See Table 7.15.

Table 7.15 Clinical details for Case 7.1

Day	Clinical observation/event	PN changes
1	Admitted to gastroenterology ward from clinic for investigation of chronic diarrhoea and weight loss. Current weight 49 kg, height 1.65 m. Usual weight 55 kg, 1.65 m. Estimated current energy requirement 1500 kcal.	
2	Contrast study revealed intestinal fistula between small bowel and transverse colon. Diarrhoea approx. 1.5 L/day.	
3	Case discussed with surgeons. For PN for 2–3 weeks prior to surgery to improve nutritional status. Patient made 'nil by mouth'. Central line inserted for PN use only.	PN prescribed (considering both fluid and electrolytes from other therapies, and potassium loss from diarrhoea of approx. 30–70 mmol/L): Volume 2 L, nitrogen 9 g, carbohydrate 400 kcal, lipid 550 kcal, Na^+ 230 mmol, K^+ 80 mmol, Ca^{2+} 5 mmol, Mg^{2+} 11 mmol, phosphate 35 mmol and micronutrients added (daily).
4	Biochemistry results: Na^+ 129 mmol/L (135–145 mmol/L), K^+ 3.2 mmol/L (3.4–5.0 mmol/L), urea 6.9 mmol/L (3.1–7.9 mmol/L), Cr 86 µmol/L (75–1550 µmol/L), corr Ca^{2+} 2.3 mmol/L (2.12–2.60 mmol/L), Mg^{2+} 0.75 mmol/L (0.7–1.0 mmol/L), phosphate 0.85 mmol/L (0.80–1.44 mmol/L). Temperature/pulse/respiration normal, diarrhoea losses reduced to 800 mL/day.	Regimen unchanged.
5	Biochemistry results: Na^+ 132 mmol/L, K^+ 3.1 mmol/L, urea 4.3 mmol/L, Cr 85 µmol/L, corr Ca^{2+} 2.2 mmol/L, Mg^{2+} 0.50 mmol/L, phosphate 0.60 mmol/L	PN regimen unchanged. Additional 20 mmol Mg^{2+} prescribed in 500 mL of saline infused over 6 h.
6	Biochemistry results: Na^+ 138 mmol/L, K^+ 3.5 mmol/L, urea 3.0 mmol/L, Cr 86 µmol/L, corr Ca 2.2 mmol/L, Mg^{2+} 0.78 mmol/L, phosphate 0.9 mmol/L. Diarrhoea reduced to 500 mL/day.	PN regimen changed to: Volume 2 L, nitrogen 11 g, carbohydrate 800 kcal, lipid 800 kcal, Na^+ 100 mmol, K^+ 80 mmol, Ca^{2+} 5 mmol, Mg^{2+} 15 mmol, phosphate 40 mmol.
7	Biochemistry results: Na^+ 139 mmol/L, K^+ 4.1 mmol/L, urea 2.8 mmol/L, Cr 78 µmol/L, Mg^{2+} 0.95 mmol/L, phosphate 1.3 mmol/L.	K^+ reduced to 60 mmol, Mg^{2+} reduced to 10 mmol, phosphate reduced to 30 mmol.

Questions

1. Calculate Mrs B's current body mass index (BMI)
2. Why were the calories provided in the initial bags less than Mrs B's requirements?
3. Why should potassium, magnesium and phosphate levels be monitored closely and explain a possible reason for the slight drop in these biochemical values on day 5?
4. Explain why the amounts of sodium and potassium were chosen in the initial formulation.
5. What additional vitamin should have been prescribed prior to PN starting?
6. Why was no extra magnesium given in the PN on day 5?
7. How much nutrition can be provided to promote weight gain and how could this be provided?

Answers

1. 18 kg/m^2.
2. Mrs B's significant weight loss, low BMI and likely malabsorption place her at risk of refeeding syndrome. An initial maximum rate of 10–20 kcal/kg is recommended. In practice, this is often achieved by administering half the patient's nutritional requirements over 24 h; however, the provision of adequate quantities of magnesium, potassium and phosphate can be problematic. It is also essential that sufficient micronutrients are provided, especially thiamine, to ensure effective metabolism of the macronutrients provided.
3. Potassium, magnesium and phosphate are all driven intracellularly during the refeeding response.
4. In 1500 mL of diarrhoea, Mrs B will lose approximately 180 mmol sodium and 38 mmol potassium; this should be added

to her basic requirements of 50 mmol sodium and 50 mmol potassium.
5. Oral thiamine or full dose intravenous vitamin B should have been prescribed to minimise the risk of refeeding syndrome.
6. Extra magnesium could not be added to the regimen on day 5 due to the stability limits for the regimen prescribed. The lipid content of the regimen places tight limits on the divalent ion content. This can be overcome by using lipid-free regimens, but this must be considered in the context of the patient's long-term nutritional plan.
7. Mrs B's predicted basic metabolic rate is only 1250 kcal. Allowing for activity, energy expenditure can be expected to increase to 1500 kcal. The provision of additional calories to promote weight gain is only appropriate if the patient is in an anabolic state and able to utilise the additional energy and nitrogen effectively to gain functional tissue. Excessive calorie intake in the face of ongoing catabolism is most likely to increase metabolic stress and increase the risk of complications such as abnormal LFTs. An additional 400–1000 kcal/day is considered sufficient to promote weight gain. The increased calories can be provided within a 3-in-1 regimen but care should be taken not to exceed the predicted glucose oxidation rate or lipid intake of 1.5 g/kg/day.

Acknowledgement

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Useful websites

British Pharmaceutical Nutrition Group. Available at: http://. www.bpng.co.uk.

American Society for Parenteral and Enteral Nutrition. Available at: http://www.nutritioncare.org/

8 Pharmacoeconomics

J. Cooke

Key points

- Expenditure on medicines is increasing at a greater rate than other health care costs.
- Increasingly governments are employing health economics to help prioritise between different medicines and other health technologies.
- In health economics, consequences of a treatment can be expressed in monetary terms (cost–benefit), natural units of effectiveness (cost-effectiveness) and in terms of patient preference or utility (cost–utility).
- Head-to-head studies offer the best way of determining overall effectiveness and cost-effectiveness.
- Sensitivity analysis can be used to address areas of uncertainty.
- Medication non-adherence, medication errors and unwanted drug effects place a considerable burden on societal health care costs.
- Decision analysis techniques offer a powerful tool for comparing alternative treatment options.

The demand for and the cost of health care are growing in all countries. Many governments are focusing their activities on promoting the effective and economic use of resources allocated to health care. The increased use of evidence-based programmes not only concentrates on optimizing health outcomes but also utilises health economic evaluations.

While there have been marked gains in life expectancy in those countries which make up the Organization for Economic Co-operation and Development (OECD), health costs have also risen in all of them. The USA spent 16% of its national income (gross domestic product, GDP) on health in 2007, a value considerably greater than many other OECD countries (Fig. 8.1).

Medicines form a small but significant proportion of total health care costs; this has been increasing consistently as new medicines are marketed. For example, the overall NHS expenditure on medicines in England in 2008 was £11.6 billion. Primary care expenditure was £8.1 million and hospital use accounted for 28.7% of the total cost at £3.3 million, up from 25.8% in 2007. The cost of medicines has increased by 3.4% overall and by 15.2% in hospitals.

Most OECD countries have seen growth in spending on medicines outstrip growth in total health spending over this period. In the USA and Australia, pharmaceutical spending has increased at more than double the rate of growth in total health spending (OECD, 2009).

There are a number of reasons why prescribing costs are increasing:

- Demographic changes have resulted in an ageing population which is living longer and has greater needs for therapeutic interventions. This patient group is more susceptible to unwanted effects of medicines which in turn consume more resources.
- More patients have complex clinical problems and co-morbidities that have higher dependency on medicines.
- Health screening programmes and improved diagnostic techniques are uncovering previously non-identified diseases, which subsequently require treatment.
- The marketing of new medicines that offer more effective and less toxic alternatives to existing agents. Invariably these are more expensive, especially biotechnology medicines, such as monoclonal antibodies which can cost in excess of £30,000 per patient per year.
- The use of existing agents becoming more widespread as additional indications for their use are found.
- Increasing numbers of standards in guidelines of care are being set by national bodies such as the National Institute for Health and Clinical Excellence (NICE).
- Public and patients have a higher expectation of their rights to access high-cost health care.
- Higher acquisition costs are also due to inflation and currency fluctuations.

In the UK, health reforms over the past decade have addressed the quality of care through promotion of quality and safety standards. The formation of NICE in 1998

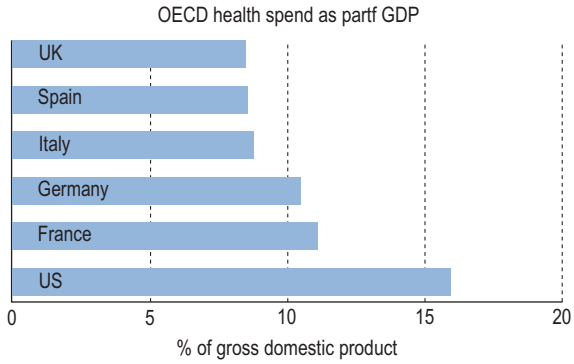

Fig. 8.1 Comparison of health spend as a percentage of gross domestic product in different countries in 2007 (OECD, 2009).

'to improve standards of patient care and to reduce inequities in access to innovative treatment' has formalised this process. NICE undertakes appraisals of medicines and other treatments (health technologies) and addresses the clinical and cost-effectiveness of therapies and compares outcomes with alternative use of NHS funds. The increased use of evidence-based programmes not only concentrates on optimizing health outcomes but also utilises health economic evaluations. Formalised health technology assessments provide an in-depth and evidence-based approach to this process.

Terms used in health economics

Pharmacoeconomics can be defined as the measurement of both the costs and consequences of therapeutic decision making. Pharmacoeconomics provides a guide for decision makers on resource allocation but does not offer a basis on which decisions should be made. Pharmacoeconomics can assist in the planning process and help assign priorities where, for example, medicines with a worse outcome may be available at a lower cost and medicines with better outcome and higher cost can be compared.

When economic evaluations are conducted it is important to categorise various costs. Costs can be direct to the organisation, that is physicians' salaries, the acquisition costs of medicines, consumables associated with drug administration, staff time in preparation and administration of medicines, laboratory charges for monitoring effectiveness and adverse drug reactions. Indirect costs include lost productivity from a disease which can manifest itself as a cost to the economy or taxation system as well as economic costs to the patient and the patient's family. All aspects of the use of medicines may be allocated costs, both direct, such as acquisition and administration costs, and indirect, such as the cost of a given patient's time off work because of illness, in terms of lost output and social security payments. The consequences of drug therapy include benefits for both the individual patient and society at large and may be quantified in terms of health outcome and quality of life, in addition to the purely economic impact.

It is worthwhile here to describe a number of definitions that further qualify costs in a health care setting. The concept of *opportunity cost* is at the centre of economics and identifies the value of opportunities which have been lost by utilizing resources in a particular service or health technology. This can be valued as the benefits that have been forsaken by investing the resources in the best alternative fashion. Opportunity cost recognises that there are limited resources available for utilising every treatment, and therefore the rationing of health care is implicit in such a system.

Average costs are the simplest way of valuing the consumption of health care resources. Quite simply, they represent the total costs (i.e. all the costs incurred in the delivery of a service) of a health care system divided by the units of production. For example, a hospital might treat 75,000 patients a year (defined as finished consultant episodes, FCEs) and have a total annual revenue cost of £150 million. The average cost per FCE is, therefore, £2000.

Fixed costs are those which are independent of the number of units of production and include heating, lighting and fixed staffing costs. *Variable costs*, on the other hand, are dependent on the numbers of units of productivity. The cost of the consumption of medicines is a good example of variable costs.

The inevitable increases in the medicines budget in a particular institute which is treating more patients, or treating those with a more complex pathology, have often been erroneously interpreted by financial managers as a failure to effectively manage the budget. To better describe the costs associated with a health care intervention, economists employ the term '*marginal costs*' to describe the costs of producing an extra unit of a particular service. The term '*incremental cost*' is employed to define the difference between the costs of alternative interventions.

Choice of comparator

Sometimes a claim is made that a treatment is cost effective. But cost effective against what? As in any good clinical trial, a treatment has to be compared against a reasonable comparator. The choice of comparator is crucial to this process. A comparator that is no longer in common use or in a dose that is not optimal will result in the evaluated treatment being seen as more effective than it actually is. Sadly many evaluations of medicines fall into this trap as sponsors seldom wish to undertake head-to-head studies against competitors. Again, the reader has to be careful when interpreting economic evaluations from settings which are different from those in local practice. A common error can be made when viewing international studies that have different health care costs and ways of treating patients and translating them directly into 'one's own practice'.

In addition, hospital charges, including those for hotel services such as heating and lighting overheads, meals and accommodation, which may constitute a major cost, should be considered. These are frequently included in an average cost per patient day.

Types of health economic evaluations

Cost–benefit analysis (CBA)

In CBA, consequences are measured in terms of the total cost associated with a programme where both costs and consequences are measured in monetary terms. While this type of analysis is preferred by economists, its use in health care is problematical as it is frequently difficult to ascribe monetary values to clinical outcomes such as pain relief, avoidance of stroke or improvements in quality of life.

Methods are available for determining cost–benefit for individual groups of patients that centre around a concept known as *contingent valuation*. Specific techniques include *willingness to pay*, where patients are asked to state how much they would be prepared to pay to avoid a particular event or symptom, for example pain or nausea following day-care surgery. Willingness to pay can be fraught with difficulties of interpretation in countries with socialised health care systems which are

invariably funded out of general taxation. *Willingness to accept* is a similar concept but is based on the minimum amount an individual person or population would receive in order to be prepared to lose or reduce a service.

CBA can be usefully employed at a macro level for strategic decisions on health care programmes. For example, a countrywide immunisation programme can be fully costed in terms of resource utilisation consumed in running the programme. This can then be valued against the reduced mortality and morbidity that occur as a result of the programme.

CBA can be useful in examining the value of services, for example centralised intravenous additive services where a comparison between a pharmacy-based intravenous additive service and ward-based preparation by doctors and nurses may demonstrate the value of the centralised pharmacy service, or a clinical pharmacokinetics service where the staffing and equipment costs can be offset against the benefits of reduced morbidity and mortality.

Cost-effectiveness analysis (CEA)

CEA can be described as an examination of the costs of two or more programmes which have the same clinical outcome as measured in physical units, for example lives saved or reduced morbidity. Treatments with dissimilar outcomes can also be analysed by this technique. Where two or more interventions have been shown to be or are assumed to be similar, then if all other factors are equal, for example convenience, side effects, availability, etc., selection can be made on the basis of cost. This type of analysis is called cost-minimisation analysis (CMA). CMA is frequently employed in formulary decision making where often the available evidence for a new product appears to be no better than for existing products. This is invariably what happens in practice as clinical trials on new medicines are statistically powered for equivalence as a requirement for licensing submission.

As previously described, CEA examines the costs associated with achieving a defined health outcome. While these outcomes can be relief of symptoms such as nausea and vomiting avoided, pain relieved, etc., CEA frequently employs years of life gained as a measure of the success of a particular programme. This can then offer a method of incrementally comparing the costs associated with two or more interventions. For example, consider a hypothetical case of the comparison of two drug treatments for the management of malignant disease.

Treatment 1 represents a 1-year course of treatment for a particular malignant disease. Assume that this is the current standard form of treatment and that the average total direct costs associated with this programme are £A per year. This will include the costs of the medicines, antiemetics, inpatient stay, radiology and pathology. Treatment 2 is a new drug treatment for the malignancy which as a result of comparative controlled clinical trials has demonstrated an improvement in the average life expectancy for this group of patients from 3.5 years for treatment 1 to 4.5 years for treatment 2. The average annual total costs for treatment 2 are £B. A comparative table can now be constructed.

Strategy	*Treatment costs*	*Effectiveness*
Treatment 1	£A	3.5 years
Treatment 2	£B	4.5 years

Incremental cost-effectiveness ratio:

$$= £B - £A / (4.5 - 3.5) \text{ per life year gained.}$$

Cost–utility analysis (CUA)

An alternative measurement for the consequences of a health care intervention is the concept of utility. Utility provides a method for estimating patient preference for a particular intervention in terms of the patient's state of well-being. Utility is described by an index which ranges between 0 (representing death) and 1 (perfect health). The product of utility and life years gained provides the term quality-adjusted life-year (QALY).

There are a number of methods for the calculation of utilities.

- The *Rosser–Kind matrix* relies on preferences from population samples from certain disease groups.
- The *visual analogue scale* method seeks to obtain patient preferences for their perceived disease state by scoring themselves on a line scaled between 0 and 1 as above.
- The *standard gamble* method requires individuals to choose between living the rest of their lives in their current state of health or making a gamble of an intervention which will restore them to perfect health. Failure of the gamble will result in instant death. The probabilities of the gamble are varied until there is indifference between the two events.
- The *time trade-off* method requires individuals to decide how many of their remaining years of life expectancy they would be prepared to exchange for complete health.

Using the previous model, if treatment 1 provides on average an increase of 3.5 years life expectancy but that this is valued at a utility of 0.9, then the health gain for this intervention is $0.9 \times 3.5 = 3.15$ QALYs. Similarly, if the increase in life expectancy with treatment 2 only has a utility of 0.8 (perhaps because it produces more nausea) then the health gain for this option becomes $0.8 \times 4.5 = 3.6$ QALYS. An incremental CUA can be undertaken as follows:

Strategy	*Treatment costs*	*Effectiveness*	*Utility*
Treatment 1	£A	3.5 years	0.9
Treatment 2	£B	4.5 years	0.8

Incremental cost–utility ratio:

$$= (£B - £A) / [(4.5 \times 0.8) - (3.5 \times 0.9)] \text{ per QALY gained.}$$

The calculation of QALYs provides a method which enables decision makers to compare different health interventions and assign priorities for decisions on resource allocation. However, the use of QALY league tables has provided much debate amongst stakeholders of health care as to their value and use.

According to NICE, there is no empirical basis for assigning a particular value (or values) to the cut-off between cost-effectiveness and cost-ineffectiveness. The general view is that those interventions with an incremental cost-effectiveness

ratio of less than £20,000 per QALY should be supported and that there should be increasingly strong reasons for accepting as cost-effective interventions with an incremental cost-effectiveness ratio of over £30,000 per QALY.

Costs and consequences

Discounting

Discounting is an economic term which is based mainly on a time preference that assumes individuals prefer to forego a part of the benefits of a programme if they can have those benefits now rather than fully in an uncertain future. The value of this preference is expressed by the discount rate. There is intense debate amongst health economists regarding the value for this annual discount level and whether both costs and consequences should be subjected to discounting. If a programme does not exceed 1 year then discounting is felt to be unnecessary.

Decision analysis

Decision analysis offers a method of pictorial representation of treatment decisions. If the results from clinical trials are available, probabilities can be placed within the arms of a decision tree and outcomes can be assessed in either monetary or quality units. An example of this can be found in the assessment of glycoprotein IIb/IIIa inhibitors in acute coronary syndrome (National Institute for Health and Clinical Excellence, 2002). The evidence of clinical and economic outcomes compares percutaneous coronary intervention and coronary artery bypass grafting. To populate a decision tree, it is necessary to obtain information from the literature on the probabilities for the clinical benefits and risks of each procedure (Table 8.1). The costs of the various procedures, consumables and bed stay are then calculated (Table 8.2). From these a decision tree can be constructed that determines the cost-effectiveness of one intervention over another (Fig. 8.2).

Table 8.1 Baseline probabilities used in the short-term model of percutaneous coronary intervention (PCI) versus coronary artery bypass graph (CABG; National Institute for Health and Clinical Excellence, 2002)

			Parameters of the beta distribution	
Node	Description	Probability	α	β
A	Acute PCI	0.05	53	980
B	Repeat revasc.	0.048	8	157
C	Repeat revasc. PCI	1.00	–	–
D	Death (revasc. PCI)	0.00	0.01	7.99
E	MI (revasc. PCI)	0.13	1	7
F	Death (revasc. CABG)	0.00	–	–
G	MI (revasc. CABG)	0.00	–	–
H	Death (no repeat revasc.)	0.03	5	152
I	MI (no repeat revasc.)	0.03	5	147
J	CABG	0.05	47	933
K	Death (CABG)	0.11	5	42
L	MI (CABG)	0.07	3	39
M	6-month revasc.	0.05	48	885
N	6-month revasc. PCI	0.48	23	25
O	Death (6-month revasc. PCI)	0.09	2	21
P	MI (6-month revasc. PCI)	0.10	2	19
Q	Death (6-month revasc. CABG)	0.00	0.01	24.99
R	MI (6-month revasc. CABG)	0.16	4	21

Table 8.1 Baseline probabilities used in the short-term model of percutaneous coronary intervention (PCI) versus coronary artery bypass graph (CABG; National Institute for Health and Clinical Excellence, 2002)—cont'd

			Parameters of the beta distribution	
Node	Description	Probability	α	β
S	Death (no revasc.)	0.08	68	817
T	MI (no revasc.)	0.05	40	777
	Baseline risk of gastro-intestinal bleeding:			
	(i) Undergoing PCI in acute period	0.00	0.01	52.99
	(ii) Undergoing CABG in acute period	0.02	1	46
	(iii) No initial revasc.	0.01	12	921

CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; revasc., revascularisation intervention; MI, myocardial infarction.

Table 8.2 Unit costs used in the analysis of percutaneous coronary intervention (PCI) versus coronary artery bypass graph (CABG; National Institute for Health and Clinical Excellence, 2002)

Unit cost	Unit	Base-case value
PCI	Procedure	£1410.04
CABG	Procedure	£4902.22
Repeat PCI	Per diem	£2976
Angiogram	Procedure	£748.25
Cardiac ward	Day	£157.47
Non-cardiac ward	Day	£244.00
CCU	Day	£459.04
Outpatient	Visit	£59.70
Cardiac day case	Visit	£108.58
Non-cardiac day case	Visit	£182.00
Guidewire	Item	£61.75
Stent	Item	£599.01
Guiding catheter	Item	£37.05
Blood	Unit	£85.00
Full blood count	Item	£4.00
Endoscopy	Item	£246.00
Tirofiban	12.5 mg vial	£146.11 (+VAT)
Eptifibatide	20 mg vial	£15.54 (+VAT)
Eptifibatide	75 mg vial	£48.84 (+VAT)

Table 8.2 Unit costs used in the analysis of percutaneous coronary intervention (PCI) versus coronary artery bypass graph (CABG; National Institute for Health and Clinical Excellence, 2002)—cont'd

Unit cost	Unit	Base-case value
Abciximab	10 mg vial	£280.00 (+VAT)
Omeprazole	28 tab pack 10 mg	£18.91
Clopidogrel	28 tab pack 75 mg	£35.31

CABG, coronary artery bypass graft; CCU, coronary care unit; PCI, percutaneous coronary intervention.

If there is uncertainty about the robustness of the values of the variables within the tree, they can be varied within defined ranges to see if the overall direction of the tree changes. This is referred to as *sensitivity analysis* and is one of the most powerful tools available in an economic evaluation.

Economic evaluation of medicines

A number of countries have introduced explicit guidelines for the conduct of economic evaluations of medicines. Others require economic evaluations before allowing a medicine onto an approved list or formulary. Guidelines have been published which aim to provide researchers and peer reviewers with background guidance on how to conduct an economic evaluation and how to check its quality (Drummond et al., 2005), whilst others (National Institute for Health and Clinical Excellence, 2009a,b) have set out how they incorporate health economics in the evaluation of medicines.

Risk management of unwanted drug effects

Avoiding the adverse effects of medicines has become a desirable goal of therapeutic decision makers as well as those who promote quality assurance and risk management. Not only can there be

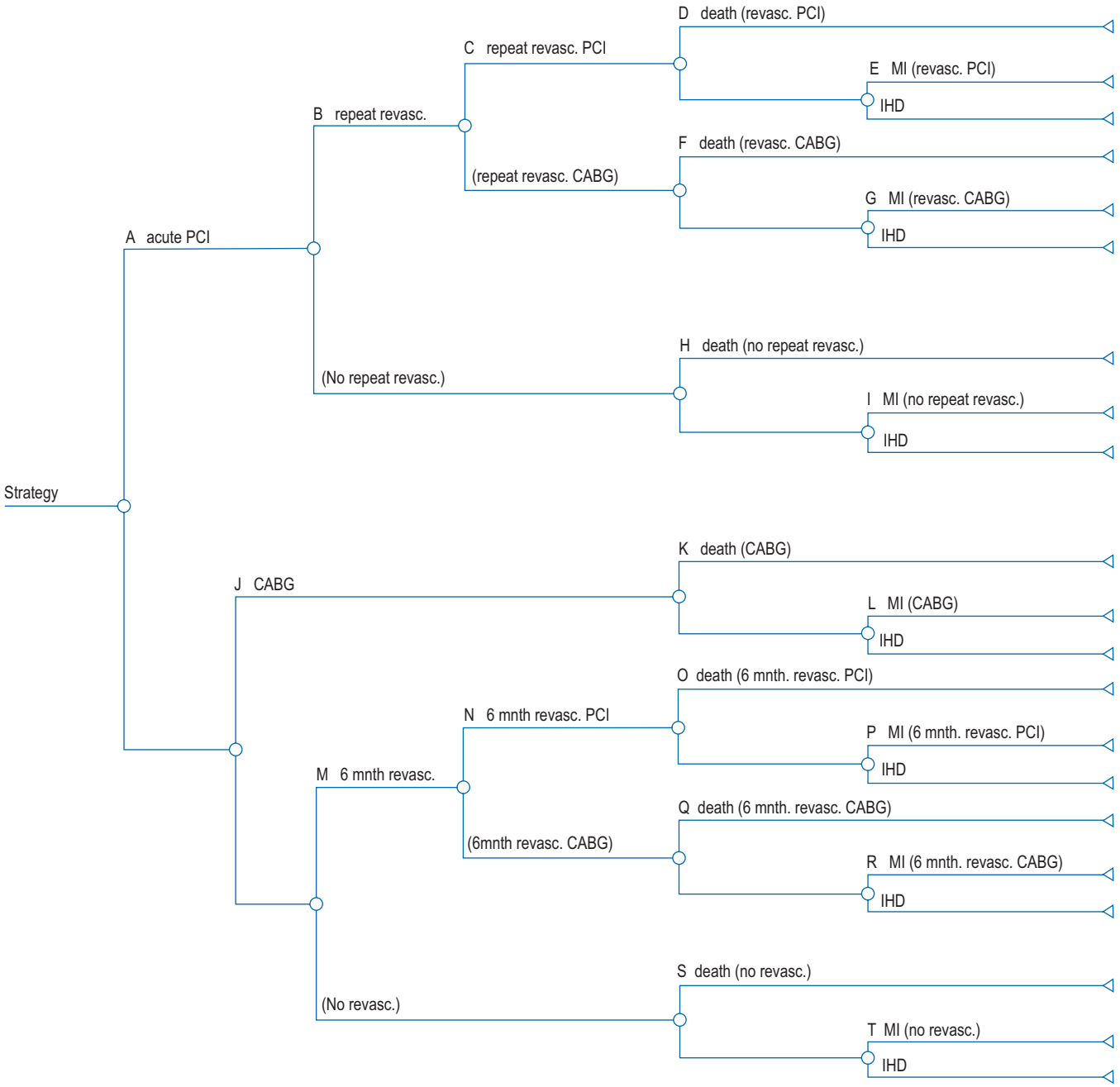

Fig. 8.2 Clinical decision tree for choices of percutaneous coronary intervention (PCI) versus coronary artery bypass graph (CABG; National Institute for Health and Clinical Excellence, 2002). MI, myocardial infarction; IHD, ischaemic heart disease; revasc., revascularisation intervention.

significant sequelae in terms of increased morbidity associated with adverse drug effects but the economic consequences can be considerable. For example, gentamicin is often regarded as a relatively inexpensive antibiotic but in the USA each case of nephrotoxicity has been reported to cost several thousands of pounds in terms of additional resources consumed even without any assessment of the reduction in a patient's quality of life. The increasingly litigious nature of society has resulted in economic valuation of perceived negligence, for example, with irreversible vestibular toxicity associated with prolonged unmonitored aminoglycoside therapy. As a result, many health care systems have targeted a significant reduction in the number of serious errors in the use of prescribed medicines.

Medication non-adherence

The costs of non-adherence with medicines are considerable. In the USA, it has been calculated that 11% of all admissions to hospital are directly associated with some form of non-adherence. This equates to two million hospital admissions a year in the USA resulting from medication non-adherence at a total cost of over £5 billion. In addition, lost work productivity through non-adherence has been estimated to cost in excess of a further £3 billion per year. The scale of the problem in the UK is probably similar.

In the UK, between a half and one-third of all medicines prescribed for long-term conditions are not taken as recommended

(Horne et al., 2005) and the estimated drug cost of unused or unwanted medicines in the NHS in England is around £100 million a year (Department of Health, 2008) annually. National guidance on medicines adherence has been issued (National Institute for Health and Clinical Excellence, 2009a,b).

Incentives and disincentives

There are good examples of both incentives and disincentives being used in the NHS to save money. In England, the contract for hospitals penalises those organisations that fail to achieve their targets for reducing *Clostridium difficile* infections. Good antimicrobial stewardship is essential for addressing this as each case of *Clostridium difficile* infection can cost at least £4000. Reduction in prescribing of both fluoroquinolones and second and third generation cephalosporins is associated with a reduction in *Clostridium difficile* infection (Department of Health and Health Protection Agency, 2008). It follows from this that reducing the use of these agents can reduce acquisition costs of the medicines.

Examples of incentives to reduce expenditure can be seen within the NHS commissioning processes in England. A typical example involves a scheme where commissioners must make 1.5% of contract value (or equivalent non-contract activity value) available for each provider's quality and innovation scheme and these include prescribing targets (Department of Health, 2010).

Conclusion

A fundamental element of the use of pharmacoeconomics in practice is the viewpoint from which the analysis is conducted. Ideally this should be from a societal perspective but frequently it is from a government or Department of Health viewpoint. Purchasers of health care may also have a different perspective from provider units, and the viewpoint of clinicians may differ from that of the patient. The pharmaceutical industry will probably have another viewpoint that will be focused on their particular products. As a consequence, with all economic evaluations the perspective from which they have been analysed should be clear.

The effect of having budgets that are rigorously defended in every section of the health service, as occurs with the medicines budget, is to deny the application of economic decision making in the most efficient way for the population served. It is clear that pharmacoeconomics has an important part to play in the practice of therapeutics (Box 8.1) and needs to be an integral part of all planned therapeutic developments.

Box 8.1 Ten examples of the application of pharmacoeconomics in practice

- The value of one treatment over another in terms of the cost for each unit of health gained
- Avoidance of costs associated with the failure to use an appropriate medicine, for example antimicrobial surgical prophylaxis
- Avoidance of the costs of the side effects or adverse effects of a medicine
- Financial planning and horizon scanning for new medicines
- Prioritisation of health care resources
- Health gain, quality of life issues and patient preferences
- Duration of care and balance between inpatient, day care and outpatient care
- Changes in legislative controls, for example reclassification of medicines from prescription only to pharmacy status
- Costs of concordance and non-concordance
- Economics of health service delivery

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