SECTION 2

LIFE STAGES

9 Neonates

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Key points

- The survival of very premature babies has been greatly increased through the use of antenatal betamethasone and neonatal surfactant treatment to prevent and treat surfactant deficiency.
- The feto-placental unit creates a unique route for drug delivery.
- Drug disposition and metabolism in the neonate are very different from those at any other time of life.
- Preterm babies grow very fast, so doses have to be re-calculated at regular intervals.
- Drug elimination in the neonate can be much slower than in children, especially in the first week, so dose intervals have to be longer.

The earliest in pregnancy at which newborn babies can sometimes survive is around 23 weeks' gestation, when survival is about 10% for liveborn babies. Conventionally, any baby born at less than 32 weeks is regarded as being at relatively high risk of death or disability. About 7.5% of all births are technically 'premature' (<37 weeks) but only 1.4% of births take place before 32 weeks of gestation. Likewise, 7% of all babies are low birth weight (LBW), for example, <2500 g, and 1.4% are very low birth weight (VLBW). However, it is the gestation at birth rather than the birth weight which is of more practical and prognostic value. The definitions of selected terms used for babies are given in Table 9.1.

Because mothers with high-risk pregnancies will often be transferred for delivery to a hospital capable of providing neonatal intensive care, the proportion of preterm and LBW babies cared for in such units is greater than in smaller maternity units in peripheral hospitals. In the population as a whole, between 1% and 2% of all babies will receive intensive care, and the most common reason for this among preterm babies is the need for respiratory support of some kind. Over three-quarters of babies born at 25 weeks' gestation now survive to discharge home.

Babies of less than 32 weeks' gestation invariably need some degree of special or intensive care, and generally go home when they are feeding adequately, somewhere between 35 and 40 weeks of postmenstrual age. So although in epidemiological terms the neonatal period is up to the first 28 postnatal days, babies may be 'neonatal' inpatients for as long as 3 or 4 months; during this time their weight may triple and their physiology and metabolism will change dramatically.

Drug disposition

Absorption

An important and unique source of drug absorption, available until birth, is the placenta. Maternal drugs pass to the fetus and back again during pregnancy, but from delivery, any drugs present in the neonatal circulation can no longer be eliminated by that route and must be dealt with by the baby's own systems. Important examples of maternal drugs which may adversely affect the newborn baby include opiates given for pain relief during labour, β-blockers given for pregnancy-induced hypertension and benzodiazepines for eclamptic seizures. In addition, a mother may be given a drug with the intention of treating not her but her fetus. An example of this is the use of corticosteroids to promote fetal lung maturation when preterm delivery is planned or expected. In this situation, betamethasone is normally the drug of choice as prednisolone is metabolised in the placenta and does not reach the fetus.

Enteral drug absorption is erratic in any newborn baby and unavailable in the ill baby because the stomach does not always empty effectively. Therefore, most drugs are given intravenously to ensure maximum bioavailability. Some drugs, such as paraldehyde and diazepam (for neonatal seizures) and paracetamol (for simple analgesia), can be given rectally. The trachea may be used as the preferred route of administration when surfactant administration is required or where adrenaline (epinephrine) is given for resuscitation. The buccal route may be used to administer glucose gel in the treatment of hypoglycaemia. In the very preterm baby of 28 weeks' gestation or less, the skin is extremely thin and a poor barrier to water loss; consequently it is also permeable to substances in contact with it. This is harmful to the baby if there is prolonged skin contact with alcohol, as in chlorhexidine in 70% methylated spirit, which causes severe chemical burn and has resulted in systemic methyl alcohol poisoning. The intramuscular route is normally avoided in premature babies because of their small muscle bulk, although the notable exceptions to this are the administration of vitamin K and naloxone.

Distribution

Drugs are distributed within a baby's body as a function of their lipid and aqueous solubility, as at any other time of life. The main difference in the neonate is that the size of the body water pool under renal control is related not to the baby's

Table 9.1 Definitions of terms	
Normal length of human pregnancy (term)	37 up to 42 completed weeks of gestation
Preterm	<37 weeks of gestation at birth
Post-term	42 completed weeks onwards
Neonatal period	Up to the 28th postnatal day
Low birth weight (LBW)	<2500 g
Very low birth weight (VLBW)	<1500 g
Extremely low birth weight (ELBW)	<1000 g

surface area but to body weight. Furthermore, the absolute glomerular filtration rate increases logarithmically with post-conceptional age irrespective of the length of a baby's gestation. This has implications for predicting the behaviour of water-soluble drugs such as gentamicin. The amount of adipose tissue can vary substantially between different babies. Any baby born more than 10 weeks early, and babies of any gestation who have suffered intrauterine growth restriction, may have little body fat. Conversely, the infant of a diabetic mother may have a particularly large fat layer and this affects the retention of predominantly lipid-soluble drugs. Protein binding in the plasma is influenced by the amount of albumin available and this in turn is related to gestation, with albumin values found 12 weeks prior to term being only two-thirds of adult concentrations.

Metabolism

The metabolic fate of drugs in the newborn is not qualitatively different to that in the older child, for example, hydroxylation, oxidation and conjugation to sulphate or glucuronide. It is the efficiency with which these processes are carried out that distinguishes the baby from the older person. In addition to the immaturity of the metabolic pathways for drug disposal, drug metabolism is also affected by the physiological hyperbilirubinaemia of the newborn. The bilirubin can compete both for enzyme-binding sites and for glucuronate, and may thus affect drug metabolism for as long as unconjugated hyperbilirubinaemia persists.

Elimination

The relative immaturity of hepatic and renal function results in correspondingly slow elimination of most drugs from the neonate. This is not necessarily a problem, so long as due account is taken of the slow elimination and dose intervals are modified accordingly. It may even be a useful property, as with phenobarbital, which when given as a loading dose (usually 20 mg/kg) will remain in circulation for days in useful therapeutic quantities, often avoiding the need for further doses. On the other hand, drugs such as gentamicin and vancomycin, which have a relatively narrow therapeutic index, must be given far less frequently than in children or adults and serum drug levels must be assayed to avoid toxicity.

There has been little study of pharmacodynamics in the term or preterm neonate. Most clinicians work on the assumption that the kinetics of drug behaviour are so different in this group of patients that the pharmacodynamic properties must follow the same pattern. In practice, the most important pharmacodynamic effect is probably that of the behaviour of opiates derived from the mother in labour. Pethidine and diamorphine are the opiates most likely to cause significant respiratory depression in the neonate. Such respiratory depression can be treated with naloxone, and a special neonatal preparation (20 µcg/mL) is available. However, after birth the opiates and their metabolites have a long serum half-life in the baby whereas the naloxone is rapidly eliminated. The initial dramatic effect of naloxone can give a false sense of security, as the baby may become narcosed after a few hours following transfer to the postnatal ward. To try to prevent this late-onset narcosis, adult naloxone (400 µcg/mL) may be given intramuscularly to ensure it remains active over several hours. Even when the respiratory effects have disappeared, opiates may have prolonged behavioural effects on both mother and baby.

Major clinical disorders

Respiratory distress syndrome (RDS)

Among preterm babies the most commonly encountered disorder is RDS (also sometimes called hyaline membrane disease from its appearance on lung histology, or surfactant deficiency lung disease in recognition of the aetiology). The root cause of this disease is the lack of sufficient pulmonary surfactant at the time of birth. The condition is rare in babies born at or near term and becomes increasingly likely the more preterm a birth takes place. It is now quite unusual to see classical RDS because it is prevented both by the use of antenatal betamethasone in the mother and the postnatal administration of surfactant to babies at highest risk (see below).

Clinically, RDS is manifested by obvious difficulty with breathing, with nasal flaring, rib recession, tachypnoea and a requirement for oxygen therapy. The natural history is that RDS becomes worse over the first 2 days, reaches a plateau and then gradually improves. The use of antenatal steroid therapy to the mother, and surfactant therapy for the infant, has not only transformed the clinical course of this condition but also greatly reduced mortality.

A relatively big baby born around 32–34 weeks of gestation with mild RDS may need no more treatment than extra oxygen. In contrast, smaller, more premature or more severely affected babies need some degree of mechanical assistance: either continuous positive airway pressure by nasal prongs or full artificial ventilation through an endotracheal tube. A few babies require high inspired concentrations of oxygen (up to 100%) for several days. Fortunately, pulmonary oxygen

toxicity is not as much a problem to the neonate as it is to the adult, though it may have a causal role in the development of bronchopulmonary dysplasia. The major concern is the damage that prolonged arterial hyperoxia can do to the retina, resulting in retinopathy of prematurity. The goal is to give enough inspired oxygen to keep the arterial partial pressure within a range of about 6–12 kPa.

Mechanical ventilation is not a comfortable experience, for adults or children, but it has taken a long time to appreciate that this may also be true for premature babies. Paralysing agents such as pancuronium are sometimes given to ventilated neonates but these only prevent the baby from moving and are not sedative. Pancuronium is widely used, partly because it wears off slowly so that the baby is not suddenly destabilised. Shorter acting agents such as atracurium are often used for temporary paralysis for intubation. Whether or not the baby is paralysed, morphine is commonly given either as intermittent doses or as an infusion, to provide narcosis and analgesia to reduce the distress of neonatal intensive care.

Antenatal steroids given to the mother reduce the incidence, severity and mortality of RDS caused by surfactant deficiency. Unfortunately, it is not possible to identify and treat all mothers whose babies could benefit. Babies of less than 32 weeks' gestation gain most benefit because they are at greatest risk of death and disability from RDS. Optimum treatment is four oral doses of 6 mg betamethasone, each given 12-hourly, or two doses of 12 mg intramuscularly 24 h apart.

Similarly, the introduction of exogenous surfactant, derived from the pig or calf, has revolutionised the management of RDS. Natural surfactants derived from animals are currently more effective than artificial synthetic ones. The first dose should be given as soon as possible after birth since the earlier it is given, the greater the benefit (Soll, 1999).

There are several other important ways of treating babies in respiratory failure. Inhaled nitric oxide dilates pulmonary arterioles and lowers the excessive pulmonary blood pressure which often complicates respiratory failure. Persistent pulmonary hypertension may also complicate early onset septicaemia and meconium aspiration syndrome; in term and near-term babies, nitric oxide is both more effective than the previous drug therapies and much less likely to lead to systemic hypotension. However, it does not reduce mortality or major complications when used in babies with birth weights less than 1500 g (Van Meurs et al., 2005).

For some babies of at least 34 weeks of gestation and at least 2 kg birth weight, extracorporeal membrane oxygenation (ECMO), in which a baby is in effect put on partial heart–lung bypass for a few days, may be life-saving when ventilation and nitric oxide fails (ECMO Collaborative Trial Group., 1996).

Patent ductus arteriosus (PDA)

PDA can be a problem in the recovery phase of RDS, and usually shows itself as a secondary increase in respiratory distress and/or ventilatory requirement, an increasing oxygen requirement, wide pulse pressure and a characteristic heart murmur. Physiologically, as pressure in the pulmonary artery falls, an open duct allows blood from the aorta to flow into the pulmonary artery, which engorges the lungs and reduces their compliance, while putting strain on the heart. Echocardiography is used to confirm the clinical suspicion. About one-third of all babies with birth weights less than 1000 g will develop signs of PDA, for example, the characteristic heart murmur, but treatment is only needed when the baby is haemodynamically compromised. When treatment is needed the options are either medical treatment (with indometacin or ibuprofen) or surgical ligation.

Indometacin is usually given intravenously in the UK, because when given enterally its absorption is unpredictable and it may need to be given before the baby has started enteral feeds. The alternative is intravenous ibuprofen. Potential serious side effects of both drugs include renal impairment, gastric haemorrhage and gut perforation. Surgery is considered when one or more courses of medical treatment fail to close the PDA or if drugs are contraindicated for any reason. There are no good randomised controlled trials to guide clinicians on the best approach to managing PDA.

Bronchopulmonary dysplasia (BPD)

BPD, also sometimes generically known as chronic lung disease of prematurity, most frequently occurs in very immature babies who have undergone prolonged respiratory support. The factors predisposing to BPD are the degree of prematurity, the severity of RDS, infection, the occurrence of PDA, oxygen toxicity and probably intrinsic genetic factors. BPD can be defined as oxygen dependency lasting more than 28 days from birth, but this definition is not very useful in that many babies born at less than 28 weeks of gestation require oxygen for 28 days or more, but few still need it after 8 weeks. A more useful functional and epidemiological definition of established BPD is oxygen dependency at 36 weeks of postmenstrual age, in a baby born before 32 weeks.

Established BPD not severe enough to need continuing mechanical ventilation is either treated with nasal continuous positive airway pressure with or without oxygen supplementation, or if less severe again is treated with oxygen through nasal cannulae. Enough oxygen must be used to maintain an oxygen saturation high enough to control pulmonary artery pressure, while avoiding chronic low-grade hyperoxia which could contribute to retinopathy of prematurity. Optimum oxygen saturations in these babies have not been rigorously defined but the outcome of several large trials is awaited.

A chronic inflammatory process is part of the pathology of BPD, and for this reason much attention has been given to the role of corticosteroids in treating it. Steroid use generally results in a rapid fall in oxygen requirements, but does not improve mortality. Indeed, there is evidence that when dexamethasone is used within the first 1 or 2 weeks there may even be an increased rate of cerebral palsy, so one of the principal indications for steroid use is when a baby remains ventilator dependent at the age of 4 weeks or more. A wide variety of treatment regimens has been tested in trials and there is no standard approach; both the initial dose (usually between 50 and 250 µcg/kg) and the rate of reduction of dose are generally individualised to the baby. Side effects such as

hypertension and glucose intolerance are common, although mostly reversible, but the effects on growth can be more serious if steroids are given for a long time.

BPD leads to increases in both pulmonary artery pressures and lung water content. The consequent strain on the heart can lead to heart failure, with excessive weight gain, increasing oxygen requirements and clinical signs such as oedema and a cardiac 'gallop' rhythm. The first-line treatment for heart failure, as in any age group, is with diuretics. Thiazides improve pulmonary mechanics as well as treating heart failure (Brion et al., 2002). Sometimes furosemide is used but its side effects are significant urinary loss of potassium and calcium, and renal calcification. An alternative is to combine a thiazide with spironolactone which causes less calcium and potassium loss. By reducing lung water content, diuretics can also improve lung compliance and reduce the work of breathing. However, BPD is not routinely treated with diuretics, since many babies do well without them. Systemic hypertension sometimes occurs among babies with BPD and may need treatment with antihypertensive drugs such as nifedipine.

For some babies with severe BPD, in whom echocardiography demonstrates pulmonary arterial pressures close to, or greater than, systemic pressure, many neonatologists try sildenafil, as there has been considerable experience using this drug off-label to prevent pulmonary hypertensive crises in babies after cardiac surgery. However, sildenafil has very variable pharmacokinetics in babies, so the dose is difficult to define, and the commonly recommended upper limit of 2 mg/kg four times a day may not be sufficient for some babies (Ahsman et al., 2010).

Significantly preterm babies still in oxygen at 36 weeks' postmenstrual age are almost certain to need oxygen at home after discharge, and home oxygen programmes for ex-premature babies with BPD are now widespread. Most babies manage to wean off supplementary oxygen in a few months but a very few may need it for up to 2 years.

Infection

Important pathogens in the first 2 or 3 days after birth are group B β-haemolytic streptococci and a variety of Gram-negative organisms, especially *Escherichia coli*. Coagulase-negative staphylococci and *Staphylococcus aureus* are more important subsequently. In general, it is wise to use narrow-spectrum agents and short courses of antibiotics whenever possible, and to discontinue blind treatment quickly, for example, after 48 h if confirmatory evidence of bacterial infection, such as blood culture, is negative. The most serious neonatal infections are listed in Table 9.2.

Superficial candida infection is common in all babies, but systemic candida infection is a particular risk in very preterm babies receiving prolonged courses of broad-spectrum antibiotics, with central venous access, and receiving intravenous feeding. Increasingly, units are adopting policies of prophylaxis with either enteral nystatin or systemic fluconazole in the highest risk preterm babies.

It is usual to start antibiotics prophylactically whenever preterm labour is unexplained, where there has been prolonged rupture of the fetal membranes prior to delivery, and when a baby is ventilated from birth. A standard combination for such early treatment is penicillin G and an aminoglycoside, to cover group B streptococci and Gram-negative pathogens. Treatment can be stopped after 48 h if cultures prove negative. Blind treatment starting when a baby is more than 48 h old has to take account of the expected local pathogens, but will always include cover for *S. aureus*. Cephalosporins such as cefotaxime and ceftazidime have been heavily promoted for use in the blind treatment of neonatal infection on the grounds of their lower toxicity when compared to aminoglycosides, their wide therapeutic index and the absence of any need to monitor serum concentrations. Their main disadvantage is the breadth of their spectrum which may result in fungal overgrowth or the spread of resistance, although they compare favourably with ampicillin in this regard. Since courses of blind treatment are often only for 48 h, and the antibiotics can be stopped when cultures are negative, there is often no need to measure levels in babies receiving aminoglycosides, thereby negating much of the apparent advantage of cephalosporins. Moreover, there is now good evidence for giving gentamicin 24 hourly rather than more frequently, as it has similar efficacy and less potential for toxicity.

Table 9.2 Serious neonatal infections and pathogens

Septicaemia	*Staphylococcus epidermidis*, group B streptococci, *Escherichia coli*
Systemic candidiasis	*Candida* spp.
Necrotizing enterocolitis	No single causal pathogen
Osteomyelitis	*Staphylococcus aureus*
Meningitis	Group B streptococci, *E. coli*

Methicillin-resistant *S. aureus* (MRSA) has emerged as a real problem in hospitals in recent years, but there is little evidence that neonatal units are a particularly hazardous environment.

The most important active viral infection in neonates is cytomegalovirus (CMV), and the most important one from which to protect babies in the UK is vertically transmitted human immuno-deficiency virus (HIV). For CMV, which is now thought to be a major factor in non-hereditary sensorineural hearing loss, treatment is with intravenous ganciclovir and oral valganciclovir.

For HIV, the goal of management is to prevent 'vertical' transmission from mother to baby. The main strategy to combat this is to use aggressive maternal treatment throughout pregnancy to suppress the maternal viral load. Current practice is to give the baby zidovudine, as a single agent, for 4 weeks when the maternal viral load is low, or triple therapy if the load is high.

Necrotizing enterocolitis (NEC)

NEC is an important complication of neonatal intensive care, and can arise in any baby. However, it most commonly occurs in premature babies and those already ill. It is especially

associated with being small for gestational age, birth asphyxia and the presence of a PDA. Since many sick babies have multiple problems, it has been difficult to disentangle causal associations from spurious links to conditions that occur anyway in ill infants, such as the need for blood transfusion. There is general agreement that the pathophysiology is related to damage of the gut mucosa, which may occur because of hypotension or hypoxia, coupled with the presence of certain organisms in the gastro-intestinal tract that invade the gut wall to give rise to the clinical condition. It almost never arises in a baby who has never been fed, whilst early 'minimal' feeding, and initiating feeding with human breast milk, appears to be protective. Probably the most important protection that can be given exogenously is enteral probiotics (AlFaleh & Bassler, 2008).

A baby who becomes ill with NEC is often septicaemic and may present acutely with a major collapse, respiratory failure and shock, or more slowly with abdominal distension, intolerance of feeds with discoloured gastric aspirates and blood in the stool. The medical treatment is respiratory and circulatory support if necessary, antibiotics, and switching to intravenous feeding for a period of time, usually 7–10 days. One of the most difficult surgical judgements is deciding if and when to operate to remove necrotic areas of gut or deal with a perforation.

The antibiotic strategy for NEC is to cover Gram-positive, Gram-negative and anaerobic bacteria. Metronidazole is used to cover anaerobes in the UK but clindamycin is preferred in some other countries. As with other drugs, metronidazole behaves very differently in neonates compared with older children and adults, having an elimination half-life of over 20 h in term babies. The elimination half-life is up to 109 h in preterm babies, partly due to poor hepatic hydroxylation in infants born before 35 weeks' gestation. There is probably a case to be made for monitoring serum levels of this drug, but in practice this is seldom done.

Haemorrhagic disease of the newborn

Haemorrhagic disease of the newborn, better described as vitamin K-dependent bleeding, is very rare but it may cause death or disability if it presents with an intracranial bleed. Except in the case of malabsorption, it affects only breast-fed babies because they get very little vitamin K in maternal milk, and their gut bacteria do not synthesise it. Formula fed infants get sufficient vitamin K in their diet.

There are several possible strategies for giving vitamin K with a view to preventing haemorrhagic disease. An intramuscular injection of phytomenadione 1 mg (0.5 mL) can be given either to every newborn baby or selectively to babies who have certain risk factors such as instrumental delivery, preterm birth, etc. Vitamin K can be given orally, so long as an adequate number of doses is given, and this has been shown to be effective in preventing disease (Wariyar et al., 2000). Intramuscular injections are an invasive and unpleasant intervention for the baby since muscle bulk is small in the newborn, and particularly the preterm, and other structures such as the sciatic nerve can be damaged even if the intention is to give the injection into the lateral thigh. Intramuscular injections can be reserved for those babies with doubtful oral absorption, for example, all those admitted for special care, or at high risk because of enzyme-inducing maternal drugs such as anticonvulsants.

Apnoea

Apnoea is the absence of breathing. Babies (and adults) normally have respiratory pauses, but preterm babies in particular are prone to prolonged pauses in respiration of over 20 s which can be associated with significant falls in arterial oxygenation. Apnoea usually has both central and obstructive components, is often accompanied by bradycardia, and requires treatment to prevent life-threatening episodes of arterial desaturation.

Episodes of apnoea and bradycardia can be treated in three ways: intubating and mechanically ventilating the baby, giving nasal continuous positive airway pressure (nCPAP) or giving respiratory stimulants such as caffeine or doxapram. The main goal of medical treatment is to reduce the number and severity of the episodes without having to resort to artificial ventilation. Caffeine both reduces apnoea in the short term, and improves long-term outcome (Schmidt et al., 2006). Doxapram is occasionally given as an adjunct to both caffeine and nCPAP, to avoid resorting to mechanical ventilation. Most clinicians stop giving respiratory stimulants when the baby is around 34 weeks of postmenstrual age, by which time most babies will have achieved an adequate degree of cardiorespiratory stability and no longer need even the most basic forms of monitoring device.

Seizures

Seizures may arise as part of an encephalopathy, when they are accompanied by altered consciousness, or as isolated events when the baby is neurologically normal between seizure episodes. Investigations are directed to finding an underlying cause but in about half of all term babies having fits without an encephalopathy, no underlying cause can be found.

Just as with children and adults, treatment may be needed to control an acute seizure which does not terminate quickly, or given long term to prevent the occurrence of fits. In the neonate, the first-choice anticonvulsant for the acute treatment of seizures is phenobarbital because it is effective, seldom causes respiratory depression, and is active for many hours or days because of its long elimination half-life. Diazepam is sometimes used intravenously or rectally but it upsets temperature control, causes unpredictable respiratory depression, and is very sedating compared to phenobarbital. Paraldehyde is occasionally used because it is easy to give rectally, is relatively non-sedating and short acting. It is excreted by exhalation and the smell can make the working environment quite unpleasant for staff. Phenytoin is often used when fits remain uncontrolled after two loading doses of phenobarbital (total 40 mg/kg) but is not usually given long term because of its narrow therapeutic index. When seizures are intractable, options include clonazepam, midazolam or lidocaine; the

last two are given as infusions. There is little experience with intravenous sodium valproate in the neonate. Longer term treatment is commonly with phenobarbital but after the first few postnatal months, carbamazepine or sodium valproate is more suitable.

Hypoxic–ischaemic encephalopathy (HIE), which usually results either from intrapartum asphyxia or from an antepartum insult such as placental abruption, is an important cause of seizures. Convulsions are a marker of a more severe insult; they usually occur within 24 h of birth and may last for several days, after which they spontaneously resolve. The less severely affected babies quickly return to neurological normality. No drug has been shown to improve outcome when given after the insult has occurred, but cooling a baby to between 33 and 34 °C for 72 h has been shown to improve the degree of neurodisability among survivors and has rapidly become standard therapy (Edwards et al., 2010).

The therapeutic dilemma lies in the degree of aggression with which convulsions should be treated, since no conventional anticonvulsant is very effective in reducing electrocerebral seizure activity, even when the clinical manifestations of seizures are abolished, and as stated before, convulsions tend naturally to cease after a few days. However, seizures which compromise respiratory function need to be treated to prevent serious falls in arterial oxygen tension and possible secondary neurological damage. Also, babies with frequent or continuous seizure activity are difficult to nurse and cause great distress to their parents. Therefore, in practice it is usual to try to suppress the clinical manifestation of seizure activity, and phenobarbital remains the most commonly used first-line treatment. Where a decision is taken to keep a baby on anticonvulsant medication, therapeutic drug monitoring can provide helpful information and may need to be repeated from time to time during follow-up.

Principles and Goals of Therapy

The ultimate aim of neonatal care at all levels is to maximise disability-free survival and identify treatable conditions which would otherwise compromise growth or development. It follows that potential problems should be anticipated and the complexities of intensive care should be avoided if at all possible.

Many of the drugs used in neonatal care are not licensed for such use, or are used off-label. There is a high potential for errors because of the small doses used, which sometimes calls for unusual levels of dilution when drawing up drugs. Constant vigilance, electronic prescribing and the use of specialised neonatal formularies are all important in preventing harm.

Rapid growth

Once the need for intensive care has passed, the growth of a premature baby can be very rapid indeed if the child is being fed with a high-calorie formula modified for use with preterm infants. Indeed, most babies born at 27 weeks, and weighing around 1 kg, can be expected to double their birth weight by the time they are 8 weeks old. Since the dose of all medications is calculated on the basis of body weight, constant review of dose is necessary to maintain efficacy, particularly for drugs that may be given for several weeks such as respiratory stimulants, diuretics and anticonvulsants. Conversely, all that is necessary to gradually wean a baby from a medication is to hold the dose constant so that the baby gradually 'grows out' of the drug. This practice is frequently used with diuretic medication in BPD, the need for which becomes less as the baby's somatic growth reduces the proportion of damaged lung in favour of healthy tissue.

Therapeutic drug monitoring

The assay of serum concentrations of various drugs has a place in neonatal medicine, particularly where the therapeutic index of a drug is narrow. It is routine to assay levels of antibiotics such as aminoglycosides and vancomycin, of which the trough measurement is of most value since it is accumulation of the drug which must be avoided. More rarely, it may be necessary to assay minimal inhibitory or bactericidal concentrations of antibiotics in blood or cerebrospinal fluid if serious infections are being treated, but constraints on sampling limit the frequency with which this may be undertaken.

Where phenobarbital or other anticonvulsants are given long term, intermittent measurement of serum levels can be a useful guide to increasing the dose. All these drugs have a long half-life, so it is most important that drug concentrations are not measured too early, or too frequently, to prevent inappropriate changes in dose being made before a steady state is reached.

Avoiding harm

Intramuscular injections are considered potentially harmful because of the small muscle bulk of babies. However, it is not always easy to establish venous access and occasionally it may be necessary to use the intramuscular route instead. For vaccines the intramuscular route is unavoidable.

For sick preterm infants ventilated for respiratory failure, handling of any kind is a destabilising influence, so the minimal necessary intervention should be the rule. Merely opening the doors of an incubator can destabilise a fragile baby. It is, therefore, a good practice to minimise the frequency of drug administration and to try to coordinate the doses of different medications.

Time-scale of clinical changes

In babies, the time-scale for starting drug treatments is very short because the clinical condition of any baby can change with great rapidity. For example, where a surfactant is required it should be given as soon as possible after birth to premature babies who are intubated and ventilated. Similarly, infection can be rapidly progressive, so starting antibiotics is a priority when the index of suspicion is high or where congenital bacterial infection is likely. The same applies for antiretroviral drugs when a baby is born to a mother positive for HIV, especially if the maternal viral load is high.

For the sick preterm infant, this model applies to a wide range of interventions. It is seldom possible to wait a few hours for a given drug, and this has obvious implications for the level of support required by a neonatal service.

Early urgent immunisation with hepatitis B vaccine and the administration of anti-hepatitis B immunoglobulin are very important in preventing vertical transmission of hepatits B when the mother is e-antigen positive. Of less urgency, but considerable importance, is making sure that premature babies who are still on the neonatal unit 8 weeks after birth get their routine immunisations, since these should be given according to chronological age irrespective of prematurity.

Patient and parent care

It is all too easy to take a mechanistic approach to neonatal medicine, on the grounds that premature infants cannot communicate their needs. Such an approach to therapy is inappropriate. Even when receiving intensive care, any infant who is not either paralysed or very heavily sedated does in fact respond with a wealth of cues and non-verbal communication in relation to their needs. Monitors, therefore, do not replace clinical skills, but provide supplementary information and advance warning of problems. Even the most premature babies show individual characteristics, which emphasises that individualised care is as important in this age group as in any other. In particular, neonatal pain and distress have effects on nociception and behaviour well into the childhood years.

Involvement of parents in every aspect of care is a necessary goal in neonatal clinical practice, and care is increasingly regarded as a partnership between professionals and parents rather than the province of professionals alone. Routine administration of oral medication is thus an act in which parents may be expected to participate, and for those whose baby has to be discharged home still requiring continuous oxygen, the parent will rapidly obtain complete control, with support from the hospital and the primary health care team. The growing number of babies who survive very premature birth but whose respiratory state requires continued support after discharge presents an increasing therapeutic challenge for the future.

Case studies

Case 9.1

Ms A went into labour as a result of an antepartum haemorrhage at 28 weeks of gestation. There was no time to give her steroids when she arrived at the maternity unit and her son, J, was born by vaginal delivery in good condition. However, he required intubation and ventilation at the age of 10 min to sustain his breathing; surfactant was immediately given down the endotracheal tube. He was not weighed at the time but was given intramuscular vitamin K and then taken to the special care unit. On arrival in the unit, baby J was weighed (1270 g) and placed in an incubator for warmth. He was connected to a ventilator. Blood was taken for culture and basic haematology, and he was prescribed antibiotics. A radiograph confirmed the diagnosis of respiratory distress syndrome.

Questions

1. Which antibiotic(s) would be appropriate initially for baby J?
   Over the next 2 days, baby J required modest ventilation and remained on antibiotics. A second dose of surfactant was given 12 h after the first. Parenteral feeding was commenced on day 2 as per unit policy, and on day 3 very slow continuous milk feeding into his stomach was started. Blood cultures were negative at 48 h and the antibiotics were stopped. On day 4 he was extubated into 30% oxygen.
   On day 5, baby J looked unwell with a rising oxygen requirement, increased work of breathing and poor peripheral perfusion. Examination revealed little else except that his liver was enlarged and a little firm, his pulses rather full and easy to feel and there was a moderate systolic heart murmur. One possibility was infection.
2. Which antibiotics would be appropriate for baby J on day 5?
   Another possibility was a patent arterial duct leading to heart failure.
3. How could his heart failure and patent ductus arteriosus be treated?
   After appropriate treatment he looked progressively better and when the blood culture was negative after 2 days, the antibiotics were stopped. By the age of 2 weeks, baby J was on full milk feeds and the duct had closed. He was in air. However, he began to have increasingly frequent episodes of spontaneous bradycardia, sometimes following apnoeic spells in excess of 20 s duration. Examination between episodes showed a healthy, stable baby. Investigations such as haematocrit, serum sodium and an infection screen were normal.
4. At 2 weeks, which drug of choice could be used to treat his apnoea and bradycardia? What would be the expected duration of treatment with this drug?

Answers

1. Blind antibiotic cover is usually started until negative blood cultures are received. Penicillin and gentamicin would provide good cover for streptococci and Gram-negative organisms, which are the most likely potential pathogens at this stage. A suitable dose would be 30 mg/kg of penicillin every 12 h and 2.5 mg/kg of gentamicin every 12 h. Alternatively, a third-generation cephalosporin such as cefotaxime could be used for initial blind treatment. If cultures were negative at 48 h, antibiotics could be stopped provided that there were no clinical indications to continue.
2. At day 5, antibiotic treatment should take account of the likely pathogens such as *S. aureus* and others causing nosocomial infections. A suitable choice for the former would be flucloxacillin, if there was no concern about MRSA, or vancomycin if there was. The vancomycin starting dose would be 15 mg/kg every 12 h. The addition of another agent with good Gram-negative activity such as gentamicin or a third-generation cephalosporin would provide good cover.
3. Intravenous indometacin or ibuprofen would be suitable for the treatment of patent ductus arteriosus. Furosemide (1 mg/kg as a single dose) is the drug of choice for acute heart failure.
4. Caffeine is now the drug of choice. A suitable dose of caffeine for baby J would be a loading dose of 20 mg/kg with maintenance dose of 5 mg/kg/day, increasing to 10 mg/kg/day if necessary. The frequency of episodes of apnoea and bradycardia should decline immediately. The treatment is likely to continue until he is about 34 weeks of postmenstrual age, when his control of breathing should be mature enough to maintain good respiratory function.

Case 9.2

Baby B was born at 25 weeks' gestation and was ventilated for 5 days before being extubated onto continuous positive airways pressure. On extubation she was initially in air, but now at the age of 4 weeks she is mostly in about 30% oxygen, fully fed on milk, and growing well. Her chest X-ray shows the pattern typical of chronic lung disease. One morning she is noticed to be in 45% oxygen, she has had a large weight gain and she looks quite oedematous all over.

Questions

1. What do these symptoms suggest?
   After careful evaluation, baby B is given an oral dose of furosemide 1 mg/kg, following which the oedema goes down, her weight falls and her oxygen requirement returns to 30%.
2. What are the disadvantages of giving regular furosemide in this situation?
   A thiazide diuretic and spironolactone are prescribed. Four days later, routine biochemistry tests show a sodium of 125 mmol/L.
3. What is the choice the attending team has to make?

Answers

1. The symptoms suggest heart failure. Medical examination would probably have revealed an enlarged liver, and the heart might have had a 'gallop' rhythm as well. In babies, the symptoms and signs commonly suggest both left and right ventricular failure.
2. Regular treatment with furosemide causes hypercalcuria, as well as excessive loss of sodium and potassium. Chronic hypercalcuria can lead to nephrocalcinosis. For this reason, a combination of thiazides and spironolactone is commonly used.
3. The sodium is low (but the normal range in preterm babies is 130–140 mmol/L, lower than in children and adults). That it is low is probably an effect of the diuretics. The choice lies between carrying on with the diuretics and supplementing the sodium intake, or stopping the diuretics and observing the baby for any recurrence of heart failure.

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10 Paediatrics

C. Barker, A. J. Nunn and S. Turner

Key points

- Children are not small adults.
- Patient details such as age, weight and surface area need to be accurate to ensure appropriate dosing.
- Weight and surface area may change in a relatively short time period and necessitate dose adjustment
- Pharmacokinetic changes in childhood are important and have a significant influence on drug handling and need to be considered when choosing an appropriate dosing regimen for a child.
- The ability of the child to use different dosage forms changes with age, so a range should be available, for example, oral liquid, dispersible tablets, capsules.
- The availability of a medicinal product does not mean it is appropriate for use in children.
- The use of an unlicensed medicine in children is not illegal, although it must be ensured that the choice of drug and dose is appropriate.

Paediatrics is the branch of medicine dealing with the development, diseases and disorders of children. Infancy and childhood is a period of rapid growth and development. The various organs, body systems and enzymes that handle drugs develop at different rates; hence, drug dosage, formulation, response to drugs and adverse reactions vary throughout childhood. Compared with adult medicine, drug use in children is not extensively researched and the range of licensed drugs in appropriate dosage forms is limited.

For many purposes it has been common to subdivide childhood into the following periods:

- neonate: the first 4 weeks of life
- infant: from 4 weeks to 1 year
- child: from 1 year to 12 years

For the purpose of drug dosing, children over 12 years of age are often classified as adults. This is inappropriate because many 12 year olds have not been through puberty and have not reached adult height and weight. The International Committee on Harmonization (2001) has suggested that childhood be divided into the following age ranges for the purposes of clinical trials and licensing of medicines:

- preterm newborn infant
- term newborn infants (0–27 days)
- infants and toddlers (28 days to 23 months)
- children (2–11 years)
- adolescents (12–16/18 years)

These age ranges are intended to reflect biological changes: the newborn (birth to 4 weeks) covers the climacteric changes after birth, 4 weeks to 2 years the early growth spurt, 2–11 years the gradual growth phase and 12–18 years puberty and the adolescent growth spurt to final adult height. Manufacturers of medicines and regulatory authorities are working towards standardising the age groups quoted in each product's Summary of Product Characteristics.

Demography

The 2001 census revealed that dependent children still make up a substantial number of people, at 11.7 million, but figures published by the Office for National Statistics in 2009 indicate that over the last 25 years the percentage of the population aged 16 years and under has decreased from 21% to 19%. This trend is predicted to continue and by 2033 the percentage of the population under 16 years old is predicted to be 18%. The UK census in 2011 will be the next opportunity to confirm this trend.

Children make substantial use of hospital-based services. It has been estimated that of the 14 million attendances at hospital emergency departments reported each year in England, 2.9 million were for children. At the same time there were 4.5 million outpatient attendances and 700,000 in-patient admissions. The 10 most common admission diagnoses in a specialist children's hospital over an 18-month period are shown in Table 10.1.

Congenital anomalies

Congenital anomalies remain an important cause of infant and child mortality in England and Wales, and account for an increasing proportion of infant deaths. The National Congenital Anomaly System (NCAS), established in 1964 in the wake of the thalidomide tragedy, has monitored congenital anomalies nationally in England and Wales. Registers such as NCAS are important in planning service delivery and alerting specialists to conditions where research is required. However, it relies on voluntary notifications and collaborates with local registers to improve the quality and quantity of data (see Useful Paediatric Websites at end of chapter).

Table 10.1 Top 10 diagnoses on admission to a specialist children's hospital

Ranking	Diagnosis
1	Respiratory tract infections
2	Chronic diseases of tonsils and adenoids
3	Asthma
4	Abdominal and pelvic pain
5	Viral infection (unspecified site)
6	Non-suppurative otitis media
7	Inguinal hernia
8	Unspecified head injury
9	Gastroenteritis/colitis
10	Undescended testicle

Data for 2008 are available but there is ongoing discussion about the future direction of the recording service, given the wide variability in reporting between areas with and without regional congenital anomaly registers. In 2007, a new classification of congenital anomalies was introduced to include tighter rules for deciding which congenital anomalies should be included in the Office for National Statistics report making year on year comparisons more difficult.

In 2008, there were 175 central nervous system (CNS) anomalies, for example, hydrocephalus, 282 cleft lip/palate, 932 heart and circulatory, 258 hypospadias and 225 Down's syndrome reported to NCAS.

Neural tube defects (spina bifida) are one example of devastating congenital malformations that have been influenced by public health intervention programmes. The results of a long-term study (MRC Vitamin Study Research Group, 1991) showed that folate supplementation prevented 72% of neural tube defects when given to women at high risk of having a child with a neural tube defect. Hence, folate supplementation is now part of the routine advice given in antenatal clinics.

Cancer

Cancer is very rare in childhood; around 1700 new cases are diagnosed in children less than 15 years old in the UK each year. About one-third of all childhood cancers are leukaemias and of these, about 80% are of the acute lymphoblastic type (ALL). Although rare, childhood cancer is the most common cause of death from illness in children aged between 1 and 15 years of age.

As a consequence of the technical advances in treatment and the centralisation of services in specialist centres, a much greater number of childhood cancer sufferers are surviving to adulthood.

Asthma, eczema and hay fever

Asthma, eczema and hay fever (allergic rhinitis) are among the most common chronic diseases of childhood and most of the affected children are managed in primary care. During the 1970s and 1980s there was considerable expansion of epidemiological research into these disorders, prompted mainly by concern about the increase in hospital admissions for childhood asthma despite the availability of effective anti-asthma medication. These studies failed to identify any demographic, perinatal or environmental factor which could explain more than a small proportion of the large changes in prevalence of asthma, hay fever or eczema. Incidence rates of acute asthma in children under 5 years old were reported to be 1.5 per 1000 per week in 1991; the rates for children aged 5–14 years old were 0.9 per 1000 per week. Between 1993 and 2000 the incidence rates for both groups declined, but asthma continues to be an important childhood illness placing a burden on the health service.

Infections

Despite a dramatic decline in the incidence of childhood infectious diseases during the twentieth century, they remain an important cause of ill health in childhood. Major advances in the prevention of infections have been achieved through the national childhood vaccination programme.

The importance of maintaining high vaccine uptake has been demonstrated by the resurgence of vaccine-preventable diseases where children have not been vaccinated. Adverse publicity surrounding the MMR (measles, mumps and rubella) vaccine, involving a possible association with Crohn's disease and autism, resulted in a loss of public confidence in the vaccine and a decrease in MMR coverage. This occurred in spite of rigorous scientific investigation and evidence refuting the claims. The annual coverage for MMR for 2-year olds declined from 92% in 1992 to 87% in 2000 and data for 2004 show that it dropped to 81.5%. Although this decline is far less than that seen for pertussis in the 1970s, if MMR coverage remains at this level or declines further, resurgences of MMR in primary schoolchildren will become more common. NHS information centre data revealed 85% of children in England had received the MMR vaccine in 2007/8. However, to achieve herd immunity, 95% of children need to be immunised; unless this figure is improved a measles epidemic still remains a possibility.

An important gastro-intestinal infection that appears to be increasing is infection with verotoxin-producing *Escherichia coli* (VTEC). This is important because it is the main cause of haemolytic uraemic syndrome, a severe condition which can lead to acute renal failure in children. VTEC is an example of an emerging infection. Before the 1980s it was unknown and during the 1990s reports of infection with VTEC in children in the UK tripled from 172 in 1991 to 531 in 1999. In 2009 the rates of VTEC 0157 decreased as age increased, with significantly higher rates in the 0–4 year age group (8 per 100,000) than in 5–9 year olds (4 per 100,000) and a further decrease (2 per 100,000) in the 10–19 year age group. It is a

public health priority to improve VTEC 0157 surveillance and improve diagnostic testing.

Respiratory syncytial virus (RSV) is the most important cause of lower respiratory tract infection in infants and young children in the UK, in whom it causes bronchiolitis, tracheobronchitis and pneumonia. It is responsible for seasonal outbreaks of respiratory tract infection most commonly between October and April. The main burden of disease is borne by children under 2 years and there are around 7000–10000 confirmed laboratory reports of RSV in children in England and Wales each year. During the winter months, RSV is the single greatest cause of admission to hospital in children.

Mental health disorders

Mental health disorders are another emerging concern in the child health arena. In 2004, 1 in 10 children and young people aged 5–16 years old had a clinically diagnosed mental health disorder. These included 4% with an emotional disorder such as depression or anxiety, 6% with a conduct disorder, 2% with a hyperkinetic disorder and 1% with less common disorders, for example, autism, tics.

Groups at particular high risk of psychiatric disorder include children in the care system, young people who are homeless and young offenders. Longitudinal evidence has confirmed that many child psychiatric disorders persist well into adult life. Biological, psychological and social factors all seem likely to contribute to the risk of psychiatric disorders, and may act in combination.

Drugs, smoking and alcohol

The harm that drugs, smoking and drinking can do to the health of children and young people is recognised and a number of targets have been set in an attempt to reduce prevalence. Recent figures on smoking, alcohol and drug use among young people have been provided by the NHS Information Centre in their 2008 report.

In 2008, 6% of schoolchildren smoked regularly (at least once a week). Girls are more likely to smoke than boys and the prevalence increases with age. Around 14% of 15-year olds smoke regularly compared to 0.5% of 11-year olds. However, the prevalence of smoking amongst children has halved since its peak in the mid-1990s (13% in 1996), suggesting a decline in prevalence to below government targets. In 2007, the minimum age for buying tobacco was increased from 16 years old to 18 years old.

More than half of pupils (52%) aged 11–15 years have drunk alcohol in their lifetime. In 2008, a national survey identified that the mean amount of alcohol consumed by pupils who had drunk in the last week was 14.6 units. Boys drink more than girls and older pupils drink more than younger pupils. In one large survey, 17% of pupils aged 11–15 years old admitted to being drunk in the last 4 weeks.

The prevalence of drug use has declined since 2001. In 2008, 22% of pupils said that they had ever used drugs with 33% reporting that they had ever been offered drugs. Pupils were most likely to have taken cannabis (9%). Five percent of pupils had sniffed glue or other volatile substances in the last year and 2.9% had sniffed poppers. Overall, 3.6% of pupils had taken class A drugs in the last year.

Nutrition and exercise

Health during childhood can impact upon well-being in later life. Good nutrition and physical exercise are vital both for growth and development and for preventing health complications in later life. In addition, dietary patterns in childhood and adolescence have an influence on dietary preferences and eating patterns in adulthood.

In 2000, an international definition of overweight and obesity in childhood and adolescence was proposed to help calculate internationally comparable prevalence rates of overweight and obesity in children and adolescents. The definition interprets overweight and obesity in terms of reference points for body mass index (BMI, in kg/m^2) by age and sex, and is linked to the widely used adult overweight cut-off point of 25 and adult obesity cut-off point of 30.

In 2004, it was estimated that 14% of boys and 17% of girls aged 2–15 years of age were obese. Probable reasons for a rise in overweight and obesity in children are changes in diets and an inactive lifestyle. There is evidence that obesity at an early age tends to continue to adulthood.

Being overweight is linked to the development of type 2 diabetes, high blood pressure, heart disease, stroke, certain cancers and other types of illnesses. Therefore, healthy eating is not only important in relation to weight but also contributes to reducing the risk of heart disease, stroke and some cancers in later life. It is recommended that a well-balanced diet providing all the nutrients required should include at least five portions of fruit and vegetables a day. It is now practice in many areas for infant children (aged 4–7 years) each day to be provided with a piece of free fruit during school break time.

The normal child

Growth and development are important indicators of a child's general well-being and paediatric practitioners should be aware of the normal development milestones in childhood. In the UK, development surveillance and screening of babies and children is well established through child health clinics.

Weight is one of the most widely used and obvious indicators of growth, and progress is assessed by recording weights on a percentile chart (Fig. 10.1). A weight curve for a child which deviates from the usual pattern requires further investigation. Separate recording charts are used for boys and girls and since percentile charts are usually based on observations of the white British population, adjustments may be necessary for some ethnic groups. The World Health Organization (WHO) has challenged the widely used growth charts, based on growth rates of infants fed on formula milk. In 2006, it published new growth standards based on a study of more than 8000 breast-fed babies from six countries around the world. The optimum size is now that of a breast-fed baby. Recently, new growth charts have been introduced for children

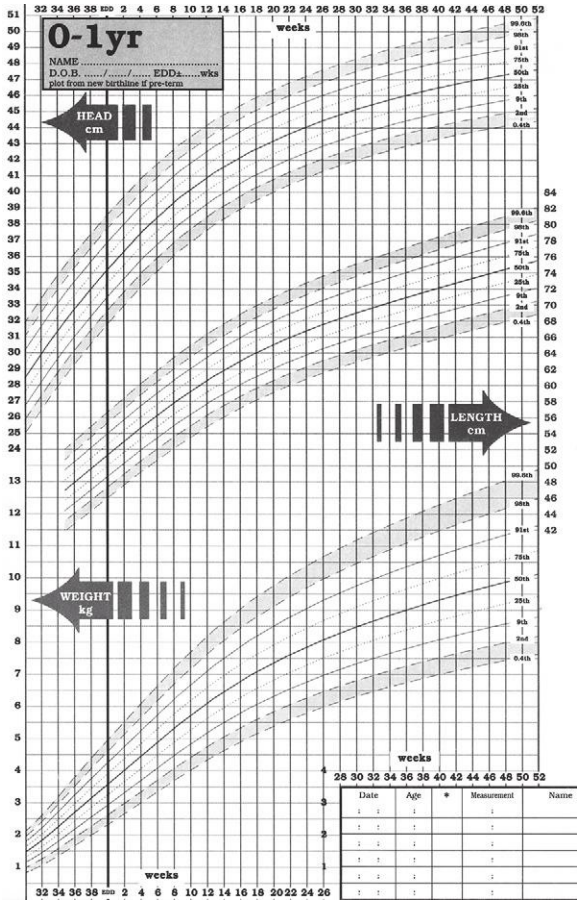

Fig. 10.1 Example of a centile chart (Child Growth Foundation).

from birth to 4 years of age. These combine the UK and WHO data. Copies can be accessed at http://www.rcpch.ac.uk/Research/UK-WHO-Growth-Charts.

Height (or length in children less than 2 years of age) is another important tool in developmental assessment. In a similar way to weight, height or length should follow a percentile line. If this is not the case or if growth stops completely, then further investigation is required. The normal rate of growth is taken to be 5 cm or more per year and any alteration in this growth velocity should be investigated.

For infants up to 2 years of age, head circumference is also a useful parameter to monitor. In addition to the above, assessments of hearing, vision, motor development and speech are undertaken at the child health clinics. A summary of age-related development is shown in Fig. 10.2.

Child health clinics play a vital role in the national childhood immunisation programme, which commences at 2 months of age. Immunisation is a major success story for preventive medicine, preventing diseases that have the potential to cause serious damage to a child's health, or even death. An example of the impact that immunisation can have on the profile of infectious diseases is demonstrated by the meningitis C immunisation campaign, which began in November 1999. The UK was the first country to introduce the meningitis C conjugate (MenC) vaccine and uptake levels have been close to 90%. The programme was targeted at under-20 year olds and has been a huge success, with a 90% reduction in cases in that age group. Authorities were hoping to mirror the success of the meningitis C campaign with the introduction of the seven valent pneumococcal vaccine into the routine UK childhood immunisation schedule in April 2006. Post-licensing surveillance has shown a large reduction in both invasive and non-invasive disease incidence due to vaccine serotypes in vaccinated individuals. However, during the same period, the UK has seen an increase in invasive disease due to the non-vaccine serotypes, caused for a large part by the six serotypes not covered by the seven valent vaccine, but present in a new 13 valent vaccine. In April 2010, the 13 valent pneumoccocal vaccine replaced the seven valent vaccine in the standard immunisation schedule. Human papilloma virus vaccine has also recently been introduced to the immunisation programme in the UK for females aged 12–13 years of age, to reduce the risk of cervical cancer.

Advice on the current immunisation schedule can be found in the current edition of the British National Formulary for Children.

Drug disposition

Pharmacokinetic factors

An understanding of the variability in drug disposition is essential if children are to receive rational and appropriate drug therapy (Anderson and Holford, 2008, 2009). For convenience, the factors that affect drug disposition will be dealt with separately. However, when treating a patient all the factors have a dynamic relationship and none should be considered in isolation.

Absorption

Oral absorption. The absorption process of oral preparations may be influenced by factors such as gastric and intestinal transit time, gastric and intestinal pH and gastrointestinal contents. Posture, disease state and therapeutic interventions such as nasogastric aspiration or drug therapy can also affect the absorption process. It is not until the second year of life that gastric acid output increases and is comparable on a per kilogram basis with that observed in adults. In addition, gastric emptying time only approaches adult values at about 6 months of age.

The bioavailability of sulphonamides, digoxin and phenobarbital has been studied in infants and children of a wide age distribution. Despite the different physicochemical properties of the drugs, a similar bioavailability pattern was observed in each case. The rate of absorption was correlated with age, being much slower in neonates than in older infants and children. However, few studies have specifically reported on the absorption process in older infants or children. The available data suggest that in older infants and children orally administered drugs will be absorbed at a rate and extent similar to those in healthy adults. Changes in the absorption rate would appear to be of minor importance when compared to the age-related differences of drug distribution and excretion.

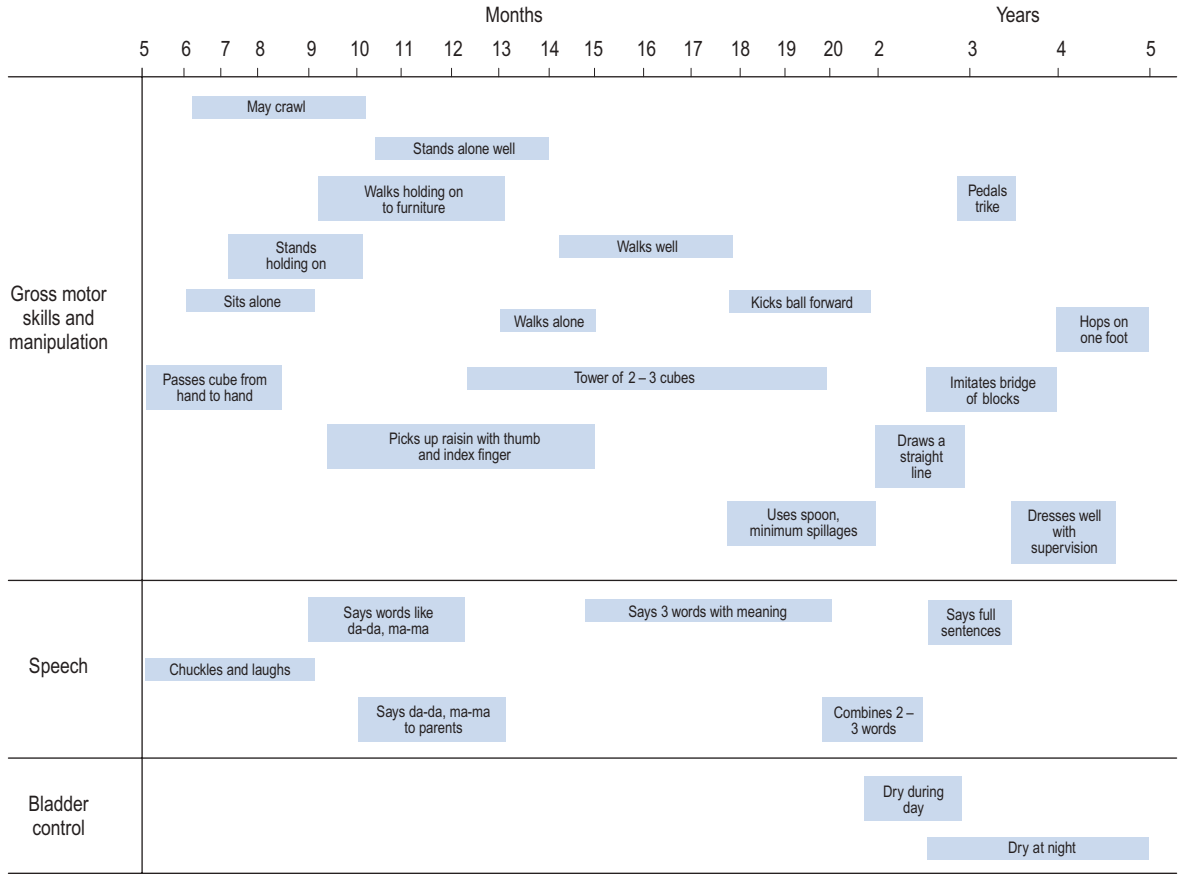

Fig. 10.2 A summary of the various stages of development.

Intramuscular absorption. Absorption in infants and children after intramuscular (i.m.) injection is noticeably faster than in the neonatal period, since muscle blood flow is increased. On a practical note, intramuscular administration is very painful and should, where possible, be avoided. The route should not be used for the convenience of staff if alternative routes of administration are available.

Intraosseous absorption. This is a useful route of administration in patients in whom intravenous access cannot be obtained. It is especially useful in paediatric cardiorespiratory arrests where rapid access is required. A specially designed needle is usually inserted into the flat tibial shaft until the marrow space is reached. This route is considered equivalent to the intravenous route for rate of drug absorption, and most drugs can be given by this route.

Topical absorption. Advances in transdermal drug delivery systems have led to an increased use of this route of administration. For example, patch formulations of hyoscine hydrobromide have been found to be very useful to dry up secretions in children with excess drooling; likewise fentanyl patches can be useful in pain management. Percutaneous absorption, which is inversely related to the thickness of the stratum corneum and directly related to skin hydration, is generally much greater in the newborn and young infant than in the adult. This can lead to adverse drug reactions (ADRs). For example, the topical application of a preparation containing prilocaine and lidocaine (EMLA) should not be used in preterm infants because of concerns about significant absorption of prilocaine in this age group, which may lead to methaemoglobinaemia. The development of needle-free subcutaneous jet injection systems appears to bring many benefits as a method of drug administration. They have been shown to give comparable levels to standard subcutaneous injections and overcome the problems of needle phobia, with less pain on administration. This system has been used with growth hormone, insulin, sedation prior to procedures and vaccination in children.

Another route of topical absorption is ophthalmically. Significant amounts of drugs may be absorbed from ophthalmic preparations through ophthalmic or nasolacrimal duct absorption; for example, administration of phenylephrine eye drops can lead to hypertensive episodes in children.

Rectal absorption. The rectal route of administration is generally less favoured in the UK than in other European countries. It can be useful in patients who are vomiting or in infants or children reluctant or unable to take oral medication. The mechanism of rectal absorption is probably similar to that of the upper part of the gastro-intestinal tract, despite differences in pH, surface area and fluid content. Although some products are erratically absorbed from the rectum, the rapid onset of action can be invaluable; for example, rectal diazepam solution produces a rapid cessation of seizures in epilepsy and can be easily administered by parents in an emergency.

Buccal absorption. The buccal cavity is a potentially useful route of administration in patients who cannot tolerate

medications via the oral route; for example, postoperative patients or those with severe nausea. Highly lipophilic drugs can rapidly cross the buccal mucosa. Fentanyl is available as a lozenge formulation (Actiq®). This has been used to relax children before painful procedures and as a treatment for breakthrough pain in palliative care patients, although it remains unlicensed for use in children. Midazolam has also been administered via this route for the acute treatment of seizures and is favoured over rectal diazepam for this purpose.

There are a number of 'melt' and 'wafer' formulations available, for example, piroxicam and ondansetron. These preparations have the advantage of palatability; however, they are not absorbed via the buccal muscosa but require swallowing and enteral absorption of the active constituent. Desmopressin for buccal absorption has been introduced as an alternative to the tablet formulation 120 µcg is given buccally compared to 200 µcg orally.

Intranasal absorption. The intranasal route is another useful route of administration. Medicines can be administered intranasally for their local action, for example, sympathomimetics, or for their systemic effects, for example, desmopressin in the treatment of diabetes insipidus. Midazolam has been widely used intranasally in children for the treatment of anxiety prior to procedures and also for the treatment of childhood seizures. Highly lipophilic analgesics such as fentanyl are used via this route for the treatment of acute pain, particularly in situations where intravenous access is difficult, for example, reduction of fractures in the emergency department. Diamorphine may be administered by nasal instillation and is preferred to intramuscular or oral morphine.

Significant systemic absorption of medicines given intranasally for their local effect can also occur; for example, corticosteroids used in the treatment of allergic rhinitis have led to cushingoid symptoms and growth suppression.

Inhalation absorption. Direct delivery of drug therapies to the lungs has been the mainstay of treatment for asthma for many years. However, systemic absorption of corticosteroids used in the treatment of asthma may produce adrenal suppression.

The administration of insulin by inhalation for the treatment of both type 1 and type 2 diabetes mellitus in adults was anticipated to be of benefit in children. The first licensed product (for adults) was launched in 2006 but was withdrawn in 2007 due to disappointing worldwide sales. No similar product has replaced it.

Distribution

A number of factors that determine drug distribution within the body are subject to change with age. These include vascular perfusion, body composition, tissue-binding characteristics and the extent of plasma protein binding.

As a percentage of total body weight, the total body water and extracellular fluid volume decrease with age (Table 10.2). Thus, for water-soluble drugs such as aminoglycosides, larger doses on a milligram per kilogram of body weight basis are required in the neonate than in the older child to achieve similar plasma concentrations.

Table 10.2 Extracellular fluid volume and total body water as a percentage of body weight at different life stages

Age	Total body water (%)	Extracellular fluid (%)
Preterm neonate	85	50
Term neonate	75	45
3 months	75	30
1 year	60	25
Adult	60	20

Protein binding. Despite normal blood pH, free fatty acid and bilirubin levels in infants, binding to plasma proteins is reduced as a result of low concentrations of both globulins and albumin. It has been suggested that binding values comparable with those seen in adults are reached within the third year of life for acidic drugs, whereas for basic drugs adult values are not reached until between 7 and 12 years of life. The clinical significance of this reduction in infants and older children is minimal. The influence of disease states, such as renal impairment, on plasma protein binding is more important.

Drug metabolism

At birth the majority of the enzyme systems responsible for drug metabolism are either absent or present in considerably reduced amounts compared with adult values, and evidence indicates that the various systems do not mature at the same time. This reduced capacity for metabolic degradation at birth is followed by a dramatic increase in the metabolic rate in the older infant and young child. In the 1–9 year age group in particular, metabolic clearance of drugs is shown to be greater than in adults, as exemplified by theophylline, phenytoin and carbamazepine. Thus, to achieve plasma concentrations similar to those observed in adults, children in this age group may require a higher dosage than adults on a milligram per kilogram basis (Table 10.3).

Metabolic pathways that play only a minor role in adults may play a more significant role in children and compensate for any deficiencies in the normal adult metabolic pathway. For example, glucuronidation accounts for up to 70% of the metabolic pathway of paracetamol in adulthood; however,

Table 10.3 Theophylline dosage in children older than 1 year

Age	Dosage (mg/kg/day)
1–9 years	24
9–12 years	20
12–16 years	18
Adult	13

Table 10.4 Renal clearance of gentamicin

	Plasma half-life
Small premature infants weighing less than 1.5 kg	11.5 h
Small premature infants weighing 1.5–2 kg	8 h
Term infants and large premature infants less than 1 week of age	5.5 h
Infants 1 week to 6 months	3–3.5 h
Infants more than 6 months to adulthood	2–3 h

in the early newborn period glucuronidation is deficient, accounting for less than 20% of paracetamol metabolism. This is compensated for by a more pronounced sulphate conjugation and this leads to an apparently normal half-life in newborns. Paracetamol appears to be less toxic in children than in adults and this may be in part explained by the compensatory routes of metabolism.

Renal excretion

The anatomical and functional immaturity of the kidneys at birth limits renal excretory capacity. Below 3–6 months of age the glomerular filtration rate is lower than that of adults, but may be partially compensated for by a relatively greater reduction in tubular reabsorption. Tubular function matures later than the filtration process. Generally, the complete maturation of glomerular and tubular function is reached only towards 6–8 months of age. After 8 months the renal excretion of drugs is comparable with that observed in older children and adults. Changes in renal clearance of gentamicin provide a good example of the maturation of renal function (Table 10.4).

Other factors

In addition to age-related changes in drug disposition, nutritional status and disease states can influence drug handling. High plasma clearance of antibiotics such as penicillins and aminoglycosides has been demonstrated in children with cystic fibrosis; increased elimination of furosemide has been reported in children with nephrotic syndrome, while prolonged elimination of furosemide has been reported in infants with congestive cardiac failure. Altered protein binding has been demonstrated in hepatic disease, nephrotic syndrome, malnutrition and cardiac failure.

Drug therapy in children

Dosage

Doses of medicines in children should be obtained from a paediatric dosage handbook and should not be extrapolated from the adult dose. There are a number of such texts available internationally. The information within them may be based on evidence from clinical studies in children or reflect the clinical experience of the contributors. In the UK, the BNF-C (see Further reading section) is a national formulary which includes prescribing guidelines and drug monographs. It contains information on licensed, unlicensed and off-label use of medicines. When consulting any dosage reference resource, care should be taken to identify the dosage convention being used. Most formularies use a single dose convention and indicate the number of times the dose should be repeated in a 24-h period. Other formularies indicate the total daily dose and the number of doses this is divided into. Some formularies combine both conventions. Confusing the total daily dose with the single dose to be repeated may have catastrophic consequences and the single dose convention has become the preferred convention.

While age, weight and height are the easiest parameters to measure, the changing requirement for drug dosage during childhood corresponds most closely with changes in body surface area (BSA). Nomograms which allow the surface area to be easily derived are available. There are practical problems in using the surface area method for prescribing; accurate height and weight may be difficult to obtain in a sick child, and manufacturers rarely provide dosage information on a surface area basis. The surface area formula for children has been used to produce the percentage method, giving the percentage of adult dose required at various ages and weights, although use should be reserved for exceptional circumstances (Table 10.5).

In selecting a method of dosage calculation, the therapeutic index of the drug should be considered. For agents with

Table 10.5 Percentage of adult dose required at various ages and body weights

	Mean weight for age (lb)	Mean weight for age (kg)	Percent of adult dose
Newborn (full term)	7.7	3.5	12.5
2 months	10	4.5	15
4 months	14	6.5	20
1 year	22	10	25
3 years	33	15	33.3
7 years	50	23	50
10 years	66	30	60
12 years	86	39	75
14 years	110	50	80
16 years	128	58	90
Adult	150	68	100

a narrow therapeutic index, such as cytotoxic agents, where recommendations are quoted per square metre, dosing must be based on the calculated surface area. However, there may be exceptions, for example, in children less than 1 year of age who have a proportionally larger surface area than other age groups. In children less than 1 year, dosages of chemotherapeutic agents are often based on weight rather than surface area to prevent overestimation of the dose in this age group.

For drugs with a wide therapeutic index, such as penicillin, single doses may be quoted for a wide age range. Between these two extremes, doses are quoted in milligrams per kilogram and this is the most widely used method of calculation. Whichever method is used, the resulting dosage should be rounded sensibly to facilitate dose measurement and administration and subsequently modified according to response or adverse effects.

It is important to note that none of the available methods of dosage calculation account for the change in dosage interval that may be required because of age-related changes in drug clearance. Where possible, the use of therapeutic drug monitoring to confirm the appropriateness of a dose is recommended.

Choice of preparation

The choice of preparation and its formulation will be influenced by the intended route of administration, the age of the child, availability of preparations, other concomitant therapy and, possibly, underlying disease states. The problems of administering medicines to children were reviewed by the European Medicines Evaluation Agency (EMEA, 2005).

Buccal route

Drugs may be absorbed rapidly from the buccal cavity (the cheek pouch) or they may dissolve when administered and be swallowed and absorbed from the stomach. 'Melt®' technology, for example, desmopressin, piroxicam, ondansetron, in which the drug and flavourings are freeze-dried into a rapidly dissolving pellet, can be very useful. The 'melt' dissolves instantly into a very small volume which is difficult for the child to reject. Gels, sprays and liquids can also be administered into the buccal cavity, using drugs such as midazolam to treat seizures.

Oral route

The oral route is usually the most convenient but in an uncooperative child it can be the least reliable. Safe and effective drug therapy requires accurate administration, yet the 5-mL spoon is a difficult means of administering liquid medicines. Use of an oral syringe can provide controlled administration, ensure accurate measurement of the calculated dose and avoids the need for dilution of preparations with syrup. Use of oral syringes (which will not fit an intravenous Luer connector) are mandatory in UK practice. Concentrated formulations may be administered as oral drops in a very small volume. Although convenient, there could be significant dosage errors if drops are not delivered accurately.

In general, liquid preparations are more suitable for children under 7 years of age; there is a wide variability in the age at which children can swallow tablets and capsules but some quite young children can cope with solid dose formulations, especially mini-tablets. Some commercially available products contain excipients such as alcohol, propylene glycol and dyes that may cause adverse effects or be inappropriate for use in children with particular disease states. The osmolality and tonicity of preparations may be important; necrotizing enterocolitis (a disorder seen in the neonatal period) has been associated with many different factors including high-osmolality infant feeding formulae and pharmaceutical preparations, although a causal relationship has not been established. Oral liquids with high-osmolality or extremes of pH may irritate the stomach and should be diluted for administration. Sugar-free preparations may be necessary in the diabetic child or be desirable in other children for the prevention of dental caries. It is, however, important to be aware of the potential problems associated with substitutes for sucrose. The artificial sweetening agent aspartame, used in some preparations, should be used with caution in children with phenylketonuria because of its phenylalanine content. Other substitutes such as sorbitol and glycerol may not contribute to dental caries but produce diarrhoea if large doses are given. In these instances, a specially formulated preparation containing a higher amount of the active drug in small volume may be preferable.

Injection solutions can sometimes be administered orally, although their concentration and pH must be considered together with the presence of unsuitable excipients. Powders or small capsules may be prepared and used as an alternative. However, lactose is a common diluent in powders and caution must be exercised in children with lactose intolerance as a result of an inborn error of metabolism, or temporarily following gastro-intestinal diseases or gut surgery.

Parents are often discouraged from adding the dose of medicine to an infant's feed. Quite apart from potential interactions which may arise with milk feeds, if the entire feed is not taken a proportion of the dose will be lost. It is also important to advise parents when it is not appropriate to crush solid dosage forms (e.g. sustained-release preparations). However, it should be recognised that addition of a medicine to a food or liquid may be the only way of rendering an unpalatable medicine acceptable. Whenever possible, evidence that this is pharmaceutically acceptable should be sought.

Manufacturers are increasingly recognising the difficulties associated with administration of medicines to children and are responding with novel formulations.

Mini tablets of just a few millimetres diameter may be useful to ease administration and allow flexibility of dosage. They may be presented in capsules or counted from bulk and can be individually coated for positioned or sustained release. Increased surface area may present larger quantities of excipients to the child and requires careful control.

If an age-appropriate formulation is not available, for example, for a medicine used off-label, a liquid oral preparation

may be prepared extemporaneously, often by crushing the 'adult' tablets and suspending the powder in commercial or locally produced suspending agents. Alternatively the 'adult' dosage form may be manipulated, for example, by splitting tablets. Due consideration must be given to safety, accuracy and stability, when modifying dosage forms.

Nasogastric and gastrostomy administration

Medicines may be administered into the stomach via a nasogastric tube in the unconscious child or when swallowing is difficult. A gastrostomy tube may be placed into the stomach transcutaneously if the problem is long term, for example, in some children with cerebral palsy. Enteral nutrition may also be administered through such tubes. Drugs such as phenytoin may adsorb to the plastic of the tubes and interact with enteral feeds, requiring special administration techniques to ensure bioavailability. Suitability of drugs for nasogastric or gastrostomy tube administration should always be checked.

Intranasal route

Several drugs, such as desmopressin, diamorphine, fentanyl and midazolam, have been shown to be absorbed from the nasal mucosa. This route may avoid the need for injections but administration may be difficult in the uncooperative child and drugs administered may irritate the mucosa or be painful.

Rectal route

Although the rectal route can be useful, it is limited by the range of products available and the dosage inflexibility associated with rectal preparations. Some oral liquid preparations such as chloral hydrate and carbamazepine can be administered rectally. The route is useful in the unconscious child in the operating theatre or intensive care unit and it is not uncommon to administer perioperative analgesics such as diclofenac and paracetamol and the antiemetic ondansetron using suppository formulations. Parents and teachers may express concerns about using this route, fearing accusations of child abuse, but it is an important route of administration for diazepam or paraldehyde in the fitting child. Increasingly, buccal administration of midazolam may be preferred.

When oral and rectal routes are inappropriate, the parenteral route may be necessary.

Parenteral route

The problems associated with the administration of intramuscular injections in infants and children have been described earlier in this chapter. The route has a limited role in paediatric drug therapy and should not be used routinely. The intravenous route of administration is more widely used, but it is still associated with a number of potential problems that are outlined below.

Intravenous access. The practical difficulties of accessing small veins in the paediatric patient do not require explanation. However, these difficulties can often explain the sites of access that are chosen. Scalp veins, commonly used in newborn infants, are often very prominent in this age group, allowing easy access. It is also more difficult for the infant to dislodge a cannula from this site than from a site on the arm or foot. Likewise the umbilical artery offers a useful route for monitoring the patient but can also be used for drug administration in some circumstances. Vasoconstrictive drugs, such as adrenaline (epinephrine), dopamine and isoprenaline, should not be given by this route.

Fluid overload. In infants and children, the direct administration of intravenous fluids from the main infusion container is associated with the risk of inadvertent fluid overload. This problem can be avoided by the use of a paediatric administration set and/or a volumetric infusion device to control the flow rate. A paediatric administration set incorporates a graduated volumetric chamber with a maximum capacity of 150 mL. Although this system is intended primarily as a safety device, the volume within the burette chamber can be readily adjusted, allowing its use for intermittent drug administration and avoiding the need for the 'piggyback system' commonly used in adult intravenous administration.

Dilution of parenteral preparations for infusion may also cause inadvertent fluid overload in children. In fluid-restricted or very young infants, it is possible that the volume of diluted drug can exceed the daily fluid requirement. In order to appreciate this problem, the paediatric practitioner should become familiar with the fluid volumes that children can tolerate. As a guide these volumes can be calculated using the following formula: 100 mL/kg for the first 10 kg, plus 50 mL/kg for the next 10 kg, plus 20 mL/kg thereafter. Worked examples are given in Table 10.6. It is important to remember that these volumes do not account for losses such as those caused by dehydration, diarrhoea or artificial ventilation. While the use of more concentrated infusion solutions may overcome the problem of fluid overload, stability data on concentrated solutions are often lacking. It may, therefore, be necessary to manipulate other therapy to accommodate the treatment or even to consider alternative treatment options. Fluid overload may also result from excessive volumes of flushing solutions and is described later. Guidance on selecting appropriate intravenous fluids for administration to children to avoid fluid induced hyponatraemia are available (National Patient Safety Agency, 2007).

Lack of suitable paediatric formulations. A large number of parenteral products are only available in adult dose sizes.

Table 10.6 Calculation of standard daily fluid requirements in paediatric patients

15 kg patient	35 kg patient
100 mL/kg × 10 kg = 1000 mL	100 mL/kg × 10 kg = 1000 mL
Plus 50 mL/kg × 5 kg = 250 mL	Plus 50 mL/kg × 10 kg = 500 mL
Total = 1250 mL/day	Plus 20 mL/kg × 15 kg = 300 mL
	Total = 1800 mL/day

The concentrations of these products can make it difficult to measure the small doses required in paediatrics. Dilution to achieve measurable concentrations, miscalculations and misinterpretation of decimal points may lead to errors. 'Ten times' errors are common particularly when drawing the dose from a single ampoule or vial that contains sufficient for an adult patient.

Displacement volume. Reconstitution of powder injections in accordance with manufacturers' directions usually makes no allowance for the displacement volume of the powder itself. Hence, the final volume may be greater than expected and the concentration will, therefore, be less than expected. This can result in the paediatric patient receiving an underdose, which becomes even more significant in younger patients receiving smaller doses or more concentrated preparations. Paediatric units usually make available modified reconstitution directions which take account of displacement volumes.

Rates of infusion. The slow infusion rates often necessary in paediatrics may influence drug therapy. The greater the distance between the administration port and the distal end of the delivery system, and the slower the flow rate, the longer the time required for the drug to be delivered to the patient. In very young infants and children, it may take several hours for the drug to reach the patient, depending on the point of injection. This is an important consideration if dosage adjustments are being made in response to plasma level monitoring. Bolus injections should always be given as close to the patient as possible.

Dead space. Following administration via an injection port, a residual amount of drug solution can remain trapped at the port. If dose volumes are small the trapped fluid may represent a considerable proportion of the intended dose. Similarly, the volume of solution required to prime the intravenous lines or the in-line filters (i.e. the dead space) can be a significant proportion of the intended dose. This problem can be minimised by ensuring that drugs are flushed at an appropriate rate into the main infusion line after administration via an injection port or through a filter, and by priming the lines initially with a compatible solution. The small volumes required to prime filters and tubing specifically designed for infants and children can be used to minimise the dead space. Modern filter materials can produce less adsorption of drugs so that more of the drug is delivered to the patient.

It is important to remember that flushing volumes can add a significant amount to the daily fluid and sodium intake, and it may be important to record the volume of flushing solutions used in patients susceptible to fluid overload.

Excipients. Analogous to oral preparations, excipients may be present in parenteral formulations and can be associated with adverse effects. Benzyl alcohol, polysorbates and propylene glycol are commonly used agents which may induce a range of adverse effects in children including metabolic acidosis, altered plasma osmolality, central nervous system depression, respiratory depression, cardiac arrhythmias and seizures. Knowledge of the products that contain these ingredients may influence drug selection.

Many hospitals have established centralised intravenous additive services (CIVAS) that prepare single intravenous doses under aseptic conditions, thus avoiding the need for preparation at ward level. Such services have not only significantly decreased the risks associated with intravenous therapy, particularly in the paediatric population, but can also produce considerable cost savings.

Pulmonary route

The use of aerosol inhalers for the prevention and treatment of asthma presents particular problems for children because of the coordination required. The availability of breath-activated devices and spacer devices and large-volume holding chambers has greatly improved the situation. Guidance has been published on the use of inhaler devices in children less than 5 years of age (National Institute for Health and Clinical Excellence, 2000) and older children (National Institute for Health and Clinical Excellence, 2002) and updated in 2008 (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2008). Recent experience has shown that different types of large-volume holding chambers alter drug delivery and absorption and should not be considered as interchangeable.

It must be remembered that drugs can be absorbed into the systemic circulation after pulmonary administration or may be absorbed by the enteral route when excess drug is swallowed. High-dose corticosteroid inhalation may suppress the adrenal cortical axis and growth by this mechanism.

Dose regimen selection

A summary of the factors to be considered when selecting a drug dosage regimen or route of administration for a paediatric patient is shown in Table 10.7.

Counselling, adherence and concordance

Parents or carers are often responsible for the administration of medicines to their children and, therefore, the concordance and adherence of both parties must be considered. Literature about non-adherence and concordance in children is limited, but the problem is considered to be widespread and similar to that reported in adults.

Non-adherence may be caused by several factors such as patient resistance to taking the medicine, complicated dosage regimens, misunderstanding of instructions and apparent ineffectiveness or side effects of treatment. In older children and adolescents who may be responsible for their own medication, different factors may be responsible for non-adherence; for example, they may be unwilling to use their medication because of peer pressure.

Several general principles should be considered in an attempt to improve adherence. Adherence is usually better when fewer medicines are prescribed. Attention should be given to the formulation, taste, appearance and ease of

Table 10.7 Factors to be considered when selecting a drug dosage regimen or route of administration for a paediatric patient

Factor	Comment
1. Age/weight/surface area	Is the weight appropriate for the stated age? If it is not, confirm the difference. Can the discrepancy be explained by the patient's underlying disease, for example, patients with neurological disorders such as cerebral palsy may be significantly underweight for their age? Is there a need to calculate dosage based on surface area, for example, cytotoxic therapy? Remember heights and weights may change significantly in children in a very short space of time. It is essential to recheck the surface area at each treatment cycle using recent heights and weights
2. Assess the appropriate dose	The age/weight of the child may have a significant influence on the pharmacokinetic profile of the drug and the manner in which it is handled. In addition, the underlying disease state may influence the dosage or dosage interval
3. Assess the most appropriate interval	In addition to the influence of disease states and organ maturity on dosage interval, the significance of the child's waking day is often overlooked. A child's waking day is generally much shorter than that of an adult and may be as little as 12 h. Instructions given to parents particularly should take account of this, for example, the instruction 'three times a day' will bear no resemblance to 'every 8 hours' in a child's normal waking day. If a preparation must be administered at regular intervals, then the need to wake the child should be discussed with the parents or preferably an alternative formulation, such as a sustained-release preparation, should be considered
4. Assess the route of administration in the light of the disease state and the preparations and formulations available	Some preparations may require manipulation to ensure their suitability for administration by a specific route. Even preparations which appear to be available in a particular form may contain undesirable excipients that require alternatives to be found, for example, patients with the inherited metabolic disorder phenylketonuria should avoid oral preparations containing the artificial sweetener aspartame because of its phenylalanine content
5. Consider the expected response and monitoring parameters	Is the normal pharmacokinetic profile altered in children? Are there any age-specific or long-term adverse effects, such as on growth, that should be monitored?
6. Interactions	Drug interactions remain as important in reviewing paediatric prescriptions as they are in adult practice. However, drug–food interactions may be more significant; particularly drug–milk interactions in babies having 5–6 milk feeds per day
7. Legal considerations	Is the drug licensed? If an unlicensed drug is to be used, the pharmacist should have sufficient information to support its use

administration of treatment. The regimen should be simple and tailored to the child's waking day. If possible the child should be involved in choosing a suitable preparation when choice is available.

Many health professionals often counsel the parents/carer only, rather than involving the child in the counselling process. Where possible, treatment goals should be set in collaboration with the child. Studies have shown that parents consider the 8–10 year age group the most appropriate at which to start including the child in the counselling process. As well as verbal instruction, parents often want written information. However, current patient information leaflets (PILs) must reflect the Summary of Product Characteristics (SmPC) and so are often inappropriate. If a drug is used in an 'off-label' manner, statements such as 'not recommended for use in children' may cause confusion and distress. Care needs to be taken, therefore, to ensure that the information provided, whether written or spoken, is appropriate for both the parent and the child.

Information provided with medicines is often complex and may not always be relevant to children. The Royal College of Paediatrics and Child Health in conjunction with other bodies have launched a range of information leaflets on medicines for parents and carers. The leaflets cover off-label use of specific drugs and aim to provide appropriate and accurate and easily understandable information on dosage and side effects to those administering medicines to children. The leaflets can be downloaded from the website: www.medicinesforchildren.org.uk

Medicines in schools

Children who are acutely ill will be treated with medicines at home or in hospital, although during their recovery phase it may be possible to return to school. Children with chronic illness such as asthma or epilepsy, and children recovering from acute illnesses, may require medicines to be administered whilst at school. In addition, there are some medical emergencies which may occur at school or on school trips that require prompt drug administration before the arrival of the emergency services. These emergencies include anaphylaxis

(associated with food allergy or insect stings), severe asthma attacks and seizures.

Policies and guidance

There is considerable controversy over the administration of medicines in schools. There is no legal or contractual duty on school staff to administer medicine or supervise a pupil taking it. This is a voluntary role. Some support staff may have specific duties to provide medical assistance as part of their contract. Policies and procedures are required to ensure that prescribed medicines are labelled, stored and administered safely and appropriately, and that teachers and care assistants are adequately trained and understand their responsibilities.

Advice has been provided for schools and their employers on how to manage medicines in schools (Department for Education and Skills, 2005). The roles and responsibilities of employers, parents and carers, governing bodies, head teachers, teachers and other staff and of local health services are all explained. The advice considers staffing issues such as employment of staff, insurance and training. Other issues covered include drawing up a health care plan for a pupil, confidentiality, record keeping, the storage, access and disposal of medicines, home-to-school transport, and on-site and off-site activities. It also provides general information on four common conditions that may require management at school: asthma, diabetes, epilepsy and anaphylaxis.

Responsibility for common medicines

Responsible pupils should be allowed to administer their own medication. Asthmatics should carry their 'reliever' inhaler (e.g. salbutamol or terbutaline), a spare should be available in school, and easy access before and during sports assured. There should be no need to have 'preventer' inhalers at school since two or three times daily administration schedules are appropriate and can avoid school hours. Medicines with a two or three times daily administration schedule should be supplied wherever possible so that dosing during school hours is avoided. Sustained-release preparations or drugs with intrinsically long half-lives may be more expensive but avoid the difficulties of administration at school. Sustained-release methylphenidate and atomoxetine, both used in the management of attention deficit hyperactivity disorder or ADHD, are examples. When administration at school is unavoidable, the school time doses can be provided in a separate, labelled container.

Special schools

Some children with severe, chronic illness will go to special rather than mainstream schools where their condition can receive attention from teachers and carers who have undergone appropriate training. Some special schools will be residential. Pupils may also attend another institution for respite care. Particular attention to communication of changes to drug treatment between parents, primary care doctors, hospital doctors and school staff is required if medication errors are to be avoided.

Monitoring parameters

Paediatric vital signs (Table 10.8) and haematological and biochemical parameters (Table 10.9) change throughout childhood and differ from those in adults. The figures presented in the tables are given as examples and may vary from hospital to hospital.

Table 10.8 Paediatric vital signs

	Age		
	<1 year	2–5 years	5–12 years
Heart rate (beats/min)	120–140	100–120	80–100
Blood pressure (systolic) (mmHg)	70–90	80–90	90–110
Respiratory rate (breaths/min)	25–45	25–30	16–25

Table 10.9 Biochemical and haematology reference ranges

	Neonate	Child	Adult
Albumin (g/L)	24–48	30–50	35–55
Bilirubin (μmol/L)	<200	<15	<17
Calcium (mmol/L)	1.8–2.8	2.15–2.7	2.20–2.55
Chloride (mmol/L)	95–110	95–110	95–105
Creatinine (μmol/L)	28–60	30–80	50–120
Haemoglobin (g/dL)	18–19	11–14	13.5–18.0 (males) 12–16 (females)
Haematocrit	0.55–0.65	0.36–0.42	0.4–0.45 (males) 0.36–0.44 (females)
Magnesium (mmol/L)	0.6–1.0	0.6–1.0	0.7–1.0
Phosphate (mmol/L)	1.3–3.0	1.0–1.8	0.85–1.4
Potassium (mmol/L)	4.0–7.0	3.5–5.5	3.5–5.0
Sodium (mmol/L)	130–145	132–145	135–145
Urea (mmol/L)	1.0–5.0	2.5–6.5	3.0–6.5
White cell count ($\times 10^9$/L)	6–15	5–14	3.5–11

Assessment of renal function

There are a number of methods of measuring renal function in children. These include the use of ^{51}Cr-EDTA, ^{99m}Tc-DTPA and using serum and urine creatinine concentrations over a timed period. However, despite some limitations, serum creatinine and estimated creatinine clearance are the most frequently used and most practical methods for day-to-day assessment of renal function.

In adults, several formulae and nomograms are available for calculating and estimating renal function. However, these cannot be extrapolated to the paediatric population; the Cockcroft and Gault equation and the estimated GFR (eGFR) equation are validated only for patients aged 18 years and over.

A number of validated models are available for use in children. These equations use combinations of serum creatinine, height, weight, BSA, age and sex to provide a simple estimate of creatinine clearance. A number of these equations have been further modified to better predict creatinine clearance; however, the advantage of simplicity is thereby lost. Several examples with their validated age ranges are shown below:

- Traub and Johnson (age 1–18 years)

$$\text{Creatinine clearance } (\text{mL/min/1.73m}^2) = \frac{42 \times \text{height (cm)}}{\text{Serum creatinine (mmol / L)}}$$

- Counahan-Barratt (age 2 months to 14 years)

$$\text{Creatinine clearance } (\text{mL/min/1.73m}^2) = \frac{38 \times \text{height (cm)}}{\text{Serum creatinine (mmol / L)}}$$

- Schwartz

$$\text{Creatinine clearance } (\text{mL/min/1.73m}^2) = \frac{k \times \text{height (cm)}}{\text{Serum creatinine (mmol / L)}}$$

where k varies dependent on the age of the patient:

low birth weight infants = 30
normal infants 0–18 months = 40
girls 2–16 years = 49
boys 2–13 years = 49
boys 13–16 years = 60

Whichever equation is chosen, it should be borne in mind that there are limitations to their use; for example, they should not be used in rapidly changing renal function, anorexic or obese patients, and they should not be taken as an accurate measure but as a guide to glomerular filtration rate.

Adverse drug reactions

The incidence of ADRs in children outside the neonatal period is thought to be less than at all other ages; however, the nature and severity of the ADRs that children experience may differ from those experienced by adults.

Studies have shown an incidence of ADRs in paediatric patients of between 0.2% and 22% of patients. The wide range reflects the limited number of formal prospective and retrospective studies examining the incidence and characteristics of ADRs in the paediatric age group and the variations in study setting, patient group and definition of ADR used. Data can also be skewed by vaccination campaigns since adverse effects are common and reporting encouraged. One consistent finding is that the greater the number of medications the child is exposed to, the greater the risk of ADRs.

ADRs in infants and older children typically occur at lower doses than in adults, and symptoms may be atypical. Examples include:

- enamel hypoplasia and permanent discolouration of the teeth with tetracyclines
- growth suppression with long-term corticosteroids in prepubertal children
- paradoxical hyperactivity in children treated with phenobarbital
- hepatotoxicity associated with the use of sodium valproate. There are three major risk factors:
  - age under 3 years
  - child receiving other anticonvulsants
  - developmental delay
- increased risk of Reye's syndrome with the use of salicylates in children with mild viral infection. Reye's syndrome is a life-threatening illness associated with drowsiness, coma, hypoglycaemia, seizures and liver failure. The mechanism of this toxicity remains unknown but aspirin should generally be avoided in children under 16 years of age.

Many ADRs occur less frequently in the paediatric population, for example, gastro-intestinal bleeds with NSAIDs, hepatotoxicity with flucloxacillin and severe skin reactions with trimethoprim/sulfamethoxazole.

The reporting of ADRs is particularly important because the current system of drug development and authorisation not only deprives children of useful drugs because of the lack of clinical trials in children but may also exclude them from epidemiological studies of ADRs to prescribed drugs. The Commission on Human Medicines strongly encourages the reporting of all suspected ADRs in children, including those relating to unlicensed or off-label use of medicines, even if the intensive monitoring symbol (an inverted black triangle) has been removed. This reporting scheme has been extended in recent years to allow pharmacists, nurses and patients/carers to report suspected ADRs.

Medication errors

In contrast to ADRs, medication errors occur as a result of human mistakes or system flaws. Medication errors are now recognised as an important cause of adverse drug events in paediatric practice and should always be considered as a possible causative factor in any unexplained situation. They can produce a variety of problems ranging from minor discomfort to death. In the USA, it is estimated that

100–150 deaths occur annually in children in hospitals due to medication errors. The actual reported incidence of errors varies considerably between studies, ranging from 0.15% to 17% of admissions. However, different reporting systems and criteria for errors make direct comparisons between studies difficult.

The incidence of medication errors and the risk of serious errors occurring in children are significantly greater than in adults. The causes are many and include:

- Heterogeneous nature of the paediatric population and the corresponding lack of standard dosage.
- Calculation errors by the prescriber, pharmacist, nurse or caregiver.
- Lack of available dosage forms and concentrations appropriate for administration to children, necessitating additional calculations and manipulations of commercially available products or preparation of extemporaneous formulations from raw materials.
- Lack of familiarity with paediatric dosing guidelines.
- Confusion between adult and paediatric preparations.
- Limited published information.
- Need for precise dose measurement and appropriate drug delivery systems; absence leads to administration errors and use of inappropriate measuring devices.
- Ten-fold dosing errors are particularly important and potentially catastrophic; but reports still appear regularly in the published literature.

The reporting and prevention of medication errors is important. The causes of medication errors are usually multifactorial and it is essential that when investigating medication errors, particular focus should be placed on system changes.

Licensing medicines for children

Medicines licensing process

All medicines marketed in the UK must have been granted a product licence (PL) under the terms of the Medicines Act 1968, or a marketing authorisation (MA) following more recent European legislation on the authorisation of medicines. The aim of licensing is to ensure that medicines have been assessed for safety, quality and efficacy. In the UK, evidence submitted by a pharmaceutical company is assessed by the Medicines and Healthcare products Regulatory Agency (MHRA) with independent advice from the Commission on Human Medicines (CHM) and its paediatric medicines expert group.

The licensed indications for a drug are published in the SmPC. Many medicines granted a product license or MA for adult use have not been scrutinised by the licensing authorities for use in children. This is reflected by contraindications or cautionary wording in the SmPC. There has been a lack of commercial incentive to develop medicines for the relatively small paediatric market and perceived difficulties in carrying out clinical trials in this group. It is not illegal to use medicines for indications or ages not specified in the data sheet but to ensure safe and effective treatment, health professionals should have adequate supporting information about the intended use before proceeding. Failure to ensure that the use of a medicine is reasonable could result in a suit for negligence if the patient comes to harm.

Unlicensed and 'off-label' medicines

It has been reported that up to 35% of drugs used in a children's hospital and 10% of drugs used in general practice may be used outside the terms of the approved, licensed indications (McIntyre et al., 2000, Turner et al., 1998). The term 'off-label' is often used to describe this. Because many of these medicines will have been produced in 'adult' dose forms, such as tablets, it is often necessary to prepare extemporaneously a suitable liquid preparation for the child. This may be made from the licensed dose form, for example, by crushing tablets and adding suitable excipients, or from chemical ingredients. An appropriate formula with a validated expiry period and ingredients to approved standards should be used. Care must be taken to ensure accurate preparation, particularly when using formulae or ingredients which are unfamiliar.

On some occasions the drug to be used has no product license or MA, perhaps because it is only just undergoing clinical trials in adults, has been imported from another country, has been prepared under a 'specials' manufacturing licence or is being used for a rare condition for which it has not previously been employed. As with 'off-label' use, there must always be information to support the quality, efficacy and safety of the medicine as well as information on the intended use. There is always a risk in using such a medicine, which must be balanced against the seriousness of the child's illness and discussed with the parents if practicable.

Many authorities require that the patient should always be informed if the medicine prescribed is unlicensed or 'off-label' and even that written informed consent be obtained before treatment begins. In many situations, in paediatrics, this would be impractical but if parents are not informed the PIL included with many medicines may cause confusion since it may state that it is 'not for use in children'. Patient or parent information specific to the situation should be prepared and provided.

Recent legislation on medicines for children

The worldwide legislation on medicines for children is changing. This is in recognition of the limited research and small number of licensed medicines brought about by a lack of incentive for commercial development. Both Europe and the USA have orphan drugs regulations designed to offer incentives for the development of medicines for rare diseases. Although not exclusively for paediatric conditions, the regulations have assisted the development of important drugs such as antiretrovirals (HIV/AIDS), alendronate (osteogenesis imperfecta), α-galactosidase (Fabry's disease), sodium phenylbutyrate (hyperammonaemia) and ibuprofen injection (closure of patent ductus arteriosus).

The USA has had regulations designed to promote the development of paediatric preparations for more than 10 years (Best Pharmaceuticals for Children Act 2002 and Pediatric Research Equity Act 2003). However, these regulations have resulted in

few significant developments in medicines for children in other countries. In the European Union, the 'European Parliament and Council Regulation (EC) on medicinal products for paediatric use' became law in January 2007. Thereafter, pharmaceutical companies wishing to market medicines for adults must agree to a Paediatric Investigation Plan with the EMEA. In return for such development, the company will receive an additional 6 months market exclusivity for its product. There are also expected to be incentives for developing paediatric formulations and indications for off-patent medicines.

Several European governments have funded paediatric clinical trials networks to stimulate research and help undertake studies resulting from the paediatric medicines regulations. In the UK, the Medicines for Children Research Network (MCRN) is part of the UK National Institute for Health Research and has six local research networks in England with equivalent provision in the other UK countries. Research and development of paediatric formulations is part of the MCRN programme.

The WHO has a 'Make medicines child size' programme to stimulate the development of age-appropriate formulations of medicines for children, particularly for those which appear in the List of Essential Medicines for Children. In June 2010, the first ever WHO model formulary for children was released to provide information on how to use over 240 essential medicines for treating illness and disease in children from 0 to 12 years of age. A number of individual countries have developed their own formularies over the years, but until now there was no single comprehensive guide for all countries (available at: http://www.who.int/childmedicines/en/).

Service frameworks

National service frameworks (NSFs) are long-term strategies for improving specific areas of care. Two paediatric service frameworks have been published; one for paediatric intensive care (Department of Health, 2002) and another for children, young people and maternity services (Department of Health, 2004) and continue to influence practice.

The service framework for paediatric intensive care defines the nature of paediatric intensive care, the elements of a high-quality paediatric intensive care service and a policy framework for the future organisation of services. Standards for district general hospitals, lead centres, major acute general hospitals and specialist hospitals are set out and cover medical and nurse staffing, facilities, and clinical effectiveness and management. Other aspects considered include retrieval services, education and training needs, and the implications for audit and research.

The framework for children, young people and maternity services sets standards for children's health and social services, and the interface of those services with education. It establishes clear standards for promoting the health and well-being of children and young people and for providing high-quality services which meet their needs.

The recommendations that relate to the use of medicines for children and young people include:

- All children and young people should receive medicines that are safe and effective, in formulations that can be easily administered and are appropriate to their age, having minimum impact on their education and lifestyle.
- Medicines should be prescribed, dispensed and administered by professionals who are well trained, informed and competent to work with children to improve health outcomes and minimise harm and any side effects of medicines.
- Children and young people and their parents or carers should be well informed and supported to make choices about their medicines and competent in the administration of medicines.

Markers of good practice are defined as:

- The use of medicines in children is based on the best available evidence of clinical use and cost-effectiveness and safety, ideally derived from clinical trials but also including, where appropriate, medicines that are not licensed for their age group or for their particular health problem ('off-label') or those that do not have a licence at all ('unlicensed') in order to achieve the best possible health outcomes and minimise harm and side effects.
- In all settings and whatever the circumstances, children and young people have equitable access to clinically safe and cost-effective medicines in age-appropriate formulations.
- Appropriate information and decision support are available for professionals who prescribe, dispense and administer medicines for children and young people.
- Children, young people and their parents/carers receive consistent, up-to-date, comprehensive, timely information on the safe and effective use of medicines.
- In all settings, professionals enable parents, young people and, where appropriate, children to be active partners in the decisions about the medicines prescribed for them.
- Primary and secondary care providers should ensure that the use of medicines in children is incorporated in their clinical governance and audit arrangements.
- The contribution of pharmacists to the effective and safe use of medicines in children is maximised.

Case studies

Case 10.1

Name: PT
Age: 7 years old
Sex: Male
Weight: 16 kg

Presenting condition:	**Presented in the emergency department with a 2-day history of worsening groin and hip pain. Could not bear weight. Patient was febrile with a temperature of 39.2°C, vomiting and dehydrated. There was no history of injury.**
Previous medical history:	**Nil of note**
Allergies:	**No known drug allergies**
Drug history:	**Nil of note**

Differential diagnosis:	**Septic arthritis, osteomyelitis**
***Tests*:**	**Urea and electrolytes** **Full blood count** **CRP, ESR** **Blood culture and sensitivities** **X-ray (hips and abdomen)** **Bone scan**
***Results*:**	**Bone scan revealed right pubic osteomyelitis** **CRP = 56 mg/L (normal range 0–10 mg/L)** **ESR = 34 mm/h (normal range 1–10 mm/h)** **Blood culture revealed *Staphylococcus aureus* sensitive to flucloxacillin**
***Prescribed*:**	**Flucloxacillin i.v. 800 mg four times a day for 2 weeks. To be followed by oral flucloxacillin 800 mg four times a day for 4 weeks**
***Progress*:**	**Temperature settled and ESR/CRP decreased following initiation of antibiotic therapy**

On the third day of treatment the patient developed a raised red rash which was suspected of being an allergic reaction to flucloxacillin. Treatment was changed to i.v. clindamycin 160 mg three times a day (10 mg/kg/dose) for 2 weeks followed by oral clindamycin 160 mg three times a day for a further 4 weeks.

Question

Comment on the drug therapy and any monitoring required.

Answer

There are a number of points to consider in this patient.

- Body weight appears low for age; therefore, need to check if the weight is correct (expected weight for a 7-year old to be approx. 23 kg). If incorrect, doses of medication will need to be recalculated.
- Recommended i.v. dose of flucloxacillin of 50 mg/kg/dose is correct. However, usual maximum oral dose of flucloxacillin is 25 mg/kg/dose. This is because of the increased risk of gastric side effects with high oral doses of flucloxacillin.
- There is a need to consider compliance with oral flucloxacillin therapy due to poor palatability of the suspension formulation (if the child would not take capsules) and the frequent dosing regimen.
- Whilst the risk of flucloxacillin-induced hepatotoxicity is low in children, there is a need to consider measuring baseline and repeat liver function tests because of the prolonged course (more than 2 weeks) of flucloxacillin therapy.
- Clindamycin has good oral bioavailability, so i.v. therapy may be unnecessary.
- The recommended dose of clindamycin by i.v. infusion is up to 10 mg/kg dose 6 hourly in severe infection. The infusion should be diluted to 6 mg/mL with sodium chloride 0.9% or dextrose 5% (or a combination) and administered over 30–60 min at a maximum rate of 20 mg/kg/h. Consider 160 mg in 27 mL sodium chloride 0.9% over 30 min.
- The recommended standard oral dose of clindamycin is 3–6 mg/kg/dose four times a day. This may contribute to problems with adherence to long-term therapy. A three times daily dosing regimen is to be preferred, particularly as this child may return to school, and four times daily dosing would require a dose to be administered at school which may be problematic.
- Consideration should be given to how to administer clindamycin. Clindamycin palmitate suspension, which was palatable, is no longer available as a licensed preparation in the UK. Whilst extemporaneous formulations are available that use clindamycin hydrochloride capsules, the palatability of the resultant suspension is a major concern, particularly given the prolonged course of therapy. A 75 mg/5 mL suspension, licensed in Belgium, can be imported. From a safety and efficacy perspective it is preferable to use such a product, which has been through a regulatory process similar to that of the UK, than to compound an extemporaneous preparation, which has not undergone appropriate pharmaceutical/pharmacokinetic evaluation.
- Consideration could be given to decreasing the dose of clindamycin to 150 mg three times a day to accommodate capsules, although the child may have difficulty taking these.
- The most serious adverse effect of clindamycin is antibiotic-associated colitis. Therefore, it is important to monitor for diarrhoea. If this arises treatment should be discontinued.

Case 10.2

Name: CS	
Age: 18 months old	
Sex: Female	
Weight: 10 kg	
Presenting condition:	**Severe right-sided abdominal pain** **Vomiting and loss of appetite** **Increased temperature 38.2°C**
Previous medical history:	**Nil of note**
Allergies:	**No known allergies**
Drug history:	**Nil of note**
Tests:	**Ultrasound**
Provisional diagnosis:	**Appendicitis**

CS went to theatre where an appendicectomy was performed. The appendix was noted to be perforated.

Prescribed:

Morphine 50 mg in 50 mL to run at 1–4 mL/h (10–40 µcg/kg/h)
Paracetamol 200 mg four times a day as required orally or per rectum
Diclofenac 12.5 mg twice a day as required per rectum.
or
Ibuprofen 100 mg four times a day as required orally when tolerating milk
Five days of i.v. antibiotic therapy with:
Gentamicin 70 mg daily
Ampicillin 250 mg four times a day
Metronidazole 75 mg three times a day

Question

Comment on the patient's drug therapy.

Answer

- The morphine dose is incorrect. If the infusion is prepared as directed, 1 mL/h will actually provide 100 µcg/kg/h. This is a 10-fold overdose which is a medication error frequently seen in children.
- There is a need to consider how to administer the appropriate rectal dose of paracetamol to this child. Often post appendicectomy patients will need to be nil by mouth for several days. Rectal bioavailability is lower than oral bioavailability and there may be a need to consider giving a larger rather than smaller paracetamol dose, that is, possibly 250 mg/rectum 8 hourly rather than 125 mg 6 hourly, for up to 48 h, but not exceeding 90 mg/kg/day.
- Suggest that paracetamol and NSAID are administered regularly in addition to the morphine for at least the first few days post-surgery. Multimodal analgesic therapy is recommended.

- There will be a need to monitor CS for side effects. Nausea, vomiting and pruritus all occur frequently with morphine but can be treated/prevented.
- Young children are particularly susceptible to developing myoclonic jerks with morphine. These are often worrying for parents but resolve on withdrawal of the morphine.
- NSAIDs are well tolerated by children and the risk of adverse events is much lower in children than the adult population. However, it is important to ensure adequate hydration status postoperatively, particularly when using NSAIDs. Acute renal failure has been reported in children who have been treated with NSAIDs and not adequately hydrated.
- The choice of antibiotics for CS is appropriate. High-dose (7 mg/kg) once-daily aminoglycoside (gentamicin/tobramycin) therapy is now routinely used in children. It is administered by short infusion over 20 min. Plasma drug levels should be monitored to achieve a 18–24 h trough level of <1 mg/L. Monitor urea and electrolytes and serum creatinine. Ampicillin can be given as a bolus injection over 3–5 min. Metronidazole should be given as a short infusion over 20 min.

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Useful websites

Child Growth Standards:
www.who.int/childgrowth/en/

Contact a Family (for families with disabled children):
www.cafamily.org.uk/

Immunization against infectious diseases:
www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/

Neonatal and Paediatric Pharmacists Group (NPPG):
www.nppg.org.uk/

Royal College of Paediatrics and Child Health:
www.rcpch.ac.uk/

The National Congenital Anomalies System:
www.statistics.gov.uk/CCI/SearchRes.asp?term=congenital+anomalies

11 Geriatrics

H. G. M. Shetty and K. Woodhouse

Key points

- The elderly form about 18% of the population and receive about one-third of health service prescriptions in the UK.
- Ageing results in physiological changes that affect the absorption, metabolism, distribution and elimination of drugs.
- Alzheimer's disease and vascular dementia are the most important diseases of cognitive dysfunction in the elderly. Donepezil, rivastigmine and galantamine are inhibitors of acetylcholinesterase and improve cognitive function in Alzheimer's disease.
- The elderly patient with Parkinson's disease is more susceptible to the adverse effects of levodopa such as postural hypotension, ventricular dysrhythmias and psychiatric effects.
- Aspirin, dipyridamole and clopidogrel reduce the reoccurrence of non-fatal strokes in the elderly.
- Treatment of elevated systolic and diastolic blood pressure in the elderly with a low dose thiazide diuretic, β-blocker, calcium antagonist or angiotensin-converting enzyme (ACE) inhibitor have all been shown to be beneficial.
- Urinary incontinence can be classified as stress incontinence, overflow incontinence or due to detrusor instability. Stress incontinence is not amenable to drug therapy. The most common drugs used in detrusor instability are oxybutynin and tolterodine.
- Non-steroidal anti-inflammatory drugs (NSAIDs) are more likely to cause gastroduodenal ulceration and bleeding in the elderly.

There has been a steady increase in the number of elderly people, defined as those over 65 years of age, since the beginning of the twentieth century. They formed only 4.8% of the population in 1901, increasing to 15.2% in 1981 and about 18% in 2001. In 2008, there were 4.8 million people over the age of 75 years in the UK. Their number is projected to increase to 5.8 million by 2018 and to 8.7 million by 2033 – a rise of 81% over 25 years. In addition, the number of people over 85 years of age is also projected to increase from 1.3 million in 2008 to 3.3 million in 2033. The number of centenarians is projected to increase from 11,000 in 2008 to 80,000 in 2033 (Office for National Statistics, 2010). The significant increase in the number of very elderly people will have important social, financial and health care planning implications.

The elderly have multiple and often chronic diseases. It is not surprising, therefore, that they are the major consumers of drugs. Elderly people receive about one-third of National Health Service (NHS) prescriptions in the UK. In most developed countries, the elderly now account for 25–40% of drug expenditure.

A survey of drug usage in 778 elderly people in the UK showed that 70% had been on prescribed medication and 40% had taken one or more prescribed drugs within the previous 24 h; 32% were taking cardiovascular drugs, and the other therapeutic categories used in decreasing order of frequency were for disorders of the central nervous system (24%), musculoskeletal system (10%), gastro-intestinal system (8%) and respiratory system (7%). The most commonly used drugs were diuretics; analgesics; hypnotics, sedatives and anxiolytics; antirheumatic drugs; and β-blockers.

Institutionalised patients tend to be on larger numbers of drugs compared with patients in the community. One study has shown that patients in long-term care facilities are likely to be receiving, on average, eight drugs. Psychotropic drugs are used widely in nursing or residential homes.

For optimal drug therapy in the elderly, a knowledge of age-related physiological and pathological changes that might affect handling of and response to drugs is essential. This chapter discusses the age-related pharmacokinetic and pharmacodynamic changes which might affect drug therapy and the general principles of drug use in the elderly.

Pharmacokinetics

Ageing results in many physiological changes that could theoretically affect absorption, first-pass metabolism, protein binding, distribution and elimination of drugs. Age-related changes in the gastro-intestinal tract, liver and kidneys are

- reduced gastric acid secretion
- decreased gastro-intestinal motility
- reduced total surface area of absorption
- reduced splanchnic blood flow
- reduced liver size
- reduced liver blood flow
- reduced glomerular filtration
- reduced renal tubular filtration.

Absorption

There is a delay in gastric emptying, reduction in gastric acid output and splanchnic blood flow with ageing. These changes do not significantly affect the absorption of the majority of drugs. Although the absorption of some drugs such as digoxin may be slower, the overall absorption is similar to that in the young.

First-pass metabolism

After absorption, drugs are transported via the portal circulation to the liver, where many lipid-soluble agents are metabolised extensively (more than 90–95%). This results in a marked reduction in systemic bioavailability. Obviously, even minor reductions in first-pass metabolism can result in a significant increase in the bioavailability of such drugs.

Impaired first-pass metabolism has been demonstrated in the elderly for several drugs, including clomethiazole, labetalol, nifedipine, nitrates, propranolol and verapamil. The clinical effects of some of these, such as the hypotensive effect of nifedipine, may be significantly enhanced in the elderly. In frail hospitalised elderly patients, that is, those with chronic debilitating disease, the reduction in pre-systemic elimination is even more marked.

Distribution

The age-related physiological changes which may affect drug distribution are

- reduced lean body mass
- reduced total body water
- increased total body fat
- lower serum albumin level
- α_1-acid glycoprotein level unchanged or slightly raised.

Increased body fat in the elderly results in an increased volume of distribution for fat-soluble compounds such as clomethiazole, diazepam, desmethyl-diazepam and thiopental. On the other hand, reduction in body water results in a decrease in the distribution volume of water-soluble drugs such as cimetidine, digoxin and ethanol.

Acidic drugs tend to bind to plasma albumin, while basic drugs bind to α_1-acid glycoprotein. Plasma albumin levels decrease with age and therefore the free fraction of acidic drugs such as cimetidine, furosemide and warfarin will increase. Plasma α_1-acid glycoprotein levels may remain unchanged or may rise slightly with ageing, and this may result in minimal reductions in free fractions of basic drugs such as lidocaine. Disease-related changes in the level of this glycoprotein are probably more important than age *per se*.

The age-related changes in distribution and protein binding are probably of significance only in the acute administration of drugs because, at steady state, the plasma concentration of a drug is determined primarily by free drug clearance by the liver and kidneys rather than by distribution volume or protein binding.

Renal clearance

Although there is a considerable interindividual variability in renal function in the elderly, in general the glomerular filtration rate declines, as do the effective renal plasma flow and renal tubular function. Because of the marked variability in renal function in the elderly, the dosages of predominantly renally excreted drugs should be individualised. Reduction in dosages of drugs with a low therapeutic index, such as digoxin and aminoglycosides, may be necessary. Dosage adjustments may not be necessary for drugs with a wide therapeutic index, for example, penicillins.

Hepatic clearance

Hepatic clearance (Cl_H) of a drug is dependent on hepatic blood flow (Q) and the steady state extraction ratio (E), as can be seen in the following formula:

$$Cl_H = Q \times \frac{C_a - C_v}{C_a} = Q \times E$$

where C_a and C_v are arterial and venous concentrations of the drug, respectively. It is obvious from the above formula that when E approaches unity, Cl_H will be proportional to and limited by Q. Drugs which are cleared by this mechanism have a rapid rate of metabolism, and the rate of extraction by the liver is very high. The rate-limiting step, as mentioned earlier, is hepatic blood flow, and therefore drugs cleared by this mechanism are called 'flow limited'. On the other hand, when E is small, Cl_H will vary according to the hepatic uptake and enzyme activity, and will be relatively independent of hepatic blood flow. The drugs which are cleared by this mechanism are termed 'capacity limited'.

Hepatic extraction is dependent upon liver size, liver blood flow, uptake into hepatocytes, and the affinity and activity of hepatic enzymes. Liver size falls with ageing and there is a decrease in hepatic mass of 20% and 40% between the third and tenth decade. Hepatic blood flow falls equally with declining liver size. Although it is recognised that the microsomal monooxygenase enzyme systems are significantly reduced in ageing male rodents, evidence suggests that this is not the case in ageing humans. Conjugation reactions have been reported to be unaffected in the elderly by some investigators, but a small decline with increasing age has been described by others.

Impaired clearance of many hepatically eliminated drugs has been demonstrated in the elderly. Morphological changes rather than impaired enzymatic activity appear to be the main cause of impaired elimination of these drugs. In frail debilitated elderly patients, however, the activities of drug-metabolising enzymes such as plasma esterases and hepatic glucuronyltransferases may well be impaired.

Pharmacodynamics

Molecular and cellular changes that occur with ageing may alter the response to drugs in the elderly. There is, however, limited information about these alterations because

of the technical difficulties and ethical problems involved in measuring them. It is not surprising, therefore, that there is relatively little information about the effect of age on pharmacodynamics.

Changes in pharmacodynamics in the elderly may be considered under two headings:

- those due to a reduction in homeostatic reserve and
- those that are secondary to changes in specific receptor and target sites.

Reduced homeostatic reserve

Orthostatic circulatory responses

In normal elderly subjects, there is blunting of the reflex tachycardia that occurs in young subjects on standing or in response to vasodilatation. Structural changes in the vascular tree that occur with ageing are believed to contribute to this observation, although the exact mechanism is unclear. Antihypertensive drugs, drugs with α receptor blocking effects (e.g. tricyclic antidepressants, phenothiazines and some butyrophenones), drugs which decrease sympathetic outflow from the central nervous system (e.g. barbiturates, benzodiazepines, antihistamines and morphine) and antiparkinsonian drugs (e.g. levodopa and bromocriptine) are, therefore, more likely to produce hypotension in the elderly.

Postural control

Postural stability is normally achieved by static reflexes, which involve sustained contraction of the musculature, and phasic reflexes, which are dynamic, short term and involve transient corrective movements. With ageing, the frequency and amplitude of corrective movements increase and an age-related reduction in dopamine (D_2) receptors in the striatum has been suggested as the probable cause. Drugs which increase postural sway, for example hypnotics and tranquillisers, have been shown to be associated with the occurrence of falls in the elderly.

Thermoregulation

There is an increased prevalence of impaired thermoregulatory mechanisms in the elderly, although it is not universal. Accidental hypothermia can occur in the elderly with drugs that produce sedation, impaired subjective awareness of temperature, decreased mobility and muscular activity, and vasodilatation. Commonly implicated drugs include phenothiazines, benzodiazepines, tricyclic antidepressants, opioids and alcohol, either on its own or with other drugs.

Cognitive function

Ageing is associated with marked structural and neurochemical changes in the central nervous system. Cholinergic transmission is linked with normal cognitive function, and in the elderly the activity of choline acetyltransferase, a marker enzyme for acetylcholine, is reduced in some areas of the cortex and limbic system. Several drugs cause confusion in the elderly. Anticholinergics, hypnotics, H_2 antagonists and β-blockers are common examples.

Visceral muscle function

Constipation is a common problem in the elderly as there is a decline in gastro-intestinal motility with ageing. Anticholinergic drugs, opiates, tricyclic antidepressants and antihistamines are more likely to cause constipation or ileus in the elderly. Anticholinergic drugs may cause urinary retention in elderly men, especially those who have prostatic hypertrophy. Bladder instability is common in the elderly, and urethral dysfunction more prevalent in elderly women. Loop diuretics may cause incontinence in such patients.

Age-related changes in specific receptors and target sites

Many drugs exert their effect via specific receptors. Response to such drugs may be altered by the number (density) of receptors, the affinity of the receptor, postreceptor events within cells resulting in impaired enzyme activation and signal amplification, or altered response of the target tissue itself. Ageing is associated with some of these changes.

α-Adrenoceptors

α_2-Adrenoceptor responsiveness appears to be reduced with ageing while α_1-adrenoceptor responsiveness appears to be unaffected.

β-Adrenoceptors

β-Adrenoceptor function declines with age. It is recognised that the chronotropic response to isoprenaline infusion is less marked in the elderly. Propranolol therapy in the elderly produces less β-adrenoceptor blocking effect than in the young. In isolated lymphocytes, studies of cyclic adenosine monophosphate (AMP) production have shown that on β-adrenoceptor stimulation the dose–response curve is shifted to the right, and the maximal response is blunted.

An age-related reduction in β-adrenoceptor density has been shown in animal adipocytes, erythrocytes and brain, and also in human lymphocytes in one study, although this has not been confirmed by other investigators. As maximal response occurs on stimulation of only 0.2% of β-adrenoceptors, a reduction in the number by itself is unlikely to account for age-related changes. Some studies have shown a reduction in high-affinity binding sites with ageing, in the absence of change in total receptor numbers, and others have suggested that there may be impairment of postreceptor transduction mechanisms with ageing that may account for reduced β-adrenoceptor function.

Cholinergic system

The effect of ageing on cholinergic mechanisms is less well known. Atropine produces less tachycardia in elderly humans than in the young. It has been shown in ageing rats that the hippocampal pyramidal cell sensitivity to acetylcholine is reduced. The clinical significance of this observation is unclear.

Benzodiazepines

The elderly are more sensitive to benzodiazepines than the young, and the mechanism of this increased sensitivity is not known. No difference in the affinity or number of benzodiazepine-binding sites has been observed in animal studies. Habituation to benzodiazepines occurs to the same extent in the elderly as in the young.

Warfarin

The elderly are more sensitive to warfarin. This phenomenon may be due to age-related changes in pharmacodynamic factors. The exact mechanism is unknown.

Digoxin

The elderly appear to be more sensitive to the adverse effects of digoxin, but not to the cardiac effects.

Common clinical disorders

This section deals in detail only with the most important diseases affecting older people. Other conditions are mentioned primarily to highlight areas where the elderly differ from the young or where modifications of drug therapy are necessary.

Dementia

Dementia is characterised by a gradual deterioration of intellectual capacity. Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies and frontotemporal dementia are the most important diseases of cognitive dysfunction in the elderly. AD has a gradual onset, and it progresses slowly. Forgetfulness is the major initial symptom. The patient has difficulty in dressing and other activities of daily living. He or she tends to get lost in his or her own environment. Eventually, the social graces are lost. VaD is the second most important cause of dementia. It usually occurs in patients in their 60s and 70s, and is more common in those with a previous history of hypertension or stroke. It is commonly associated with mood changes and emotional lability. Physical examination may reveal focal neurological deficits. A number of drugs and other conditions cause confusion in the elderly, and their effects may be mistaken for dementia. These are listed in Box 11.1.

Box 11.1 Drugs causing confusion in the elderly

- Antiparkinsonian drugs
- Barbiturates
- Benzodiazepines
- Diuretics
- Hypoglycaemic agents
- Monoamine oxidase inhibitors
- Opioids
- Steroids
- Tricyclic antidepressants

In patients with AD, damage to the cholinergic neurones connecting subcortical nuclei to the cerebral cortex has been consistently observed. Postsynaptic muscarinic cholinergic receptors are usually not affected, but ascending noradrenergic and serotonergic pathways are damaged, especially in younger patients. Based on those abnormalities, several drugs have been investigated for the treatment of AD. Lecithin, which increases acetylcholine concentrations in the brain, 4-aminopyridine, piracetam, oxitacetam and pramiracetam, all of which stimulate acetylcholine release, have been tried, but have produced no, or unimpressive, improvements in cognitive function. Anticholinesterases block the breakdown of acetylcholine and enhance cholinergic transmission. Donepezil, galantamine and rivastigmine are recommended for treatment of patients with AD of moderate severity only (those with a Mini Mental State Examination (MMSE) score of between 10 and 20 points; NICE, 2009). Donepezil is a piperidine-based acetylcholinesterase inhibitor. It has been shown to improve cognitive function in patients with mild to moderately severe AD. However, it does not improve day-to-day functioning, quality-of-life measures or rating scores of overall dementia. Rivastigmine is a non-competitive cholinesterase inhibitor. It has been shown to slow the rate of decline in cognitive and global functioning in AD. Galantamine, a reversible and competitive inhibitor of acetylcholinesterase, has also been shown to improve cognitive function significantly and is well tolerated. Adverse effects of cholinesterase inhibitors include nausea, vomiting, diarrhoea, weight loss, agitation, confusion, insomnia, abnormal dreams, muscle cramps, bradycardia, syncope and fatigue. Treatment with these drugs should only be continued in people with dementia who show an improvement or no deterioration in their minimental score, together with evidence of global (functional and behavioural) improvement after first few months of treatment. The treatment effect should then be reviewed critically every 6 months, before a decision to continue drug therapy is made.

Memantine, an *N*-methyl-D-aspartate (NMDA) antagonist, has also been used for the treatment of moderate to severe AD. It acts mainly on subtypes of glutamate receptors related to memory (i.e. NMDA), resulting in improvements in cognition. It has also been shown to have some beneficial effects on behaviour and its use is recommended in patients with moderate to severe AD as part of well-designed clinical studies (NICE, 2009).

Deposition of amyloid (in particular the peptide β/A4) derived from the Alzheimer amyloid precursor protein (APP) is an important pathological feature of the familial form of

AD that accounts for about 20% of patients. Point mutation of the gene coding for APP (located in the long arm of chromosome 21) is thought to be associated with familial AD. Future treatment strategies, therefore, might involve development of drugs which inhibit amyloidogenesis.

In some studies, donepezil and galantamine have been shown to improve cognition, behaviour and activities of daily living in patients with VaD, and in those with AD and coexistent cerebrovascular disease. Memantine has been reported to stabilise progression of VaD compared with placebo. However, acetylcholinesterase inhibitors and memantine should not be prescribed for the treatment of cognitive decline in patients with VaD, except as part of properly constructed clinical studies (National Collaborating Centre for Mental Health, 2007). Aspirin therapy has also been reported to slow the progression of VaD. The incidence of VaD is likely to decrease with other stroke prevention strategies such as smoking cessation, anticoagulation for atrial fibrillation, control of hypertension and hyperlipidemia.

Parkinsonism

Parkinsonism is a relatively common disease of the elderly with a prevalence between 50 and 150 per 100,000. It is characterised by resting tremors, muscular rigidity and bradykinesia (slowness of initiating and carrying out voluntary movements). The patient has a mask-like face, monotonous voice and walks with a stoop and a slow shuffling gait.

The elderly are more susceptible than younger patients to some of the adverse effects of antiparkinsonian drugs. Age-related decline in orthostatic circulatory responses, means that postural hypotension is more likely to occur in elderly patients with levodopa therapy. The elderly are more likely to have severe cardiac disease, and levodopa preparations should be used with caution in such patients because of the risk of serious ventricular dysrhythmias. Psychiatric adverse effects such as confusion, depression, hallucinations and paranoia occur with dopamine agonists and levodopa preparations. These adverse effects may persist for several months after discontinuation of the offending drug and may result in misdiagnosis (e.g. of AD) in the elderly. Bromocriptine and other ergot derivatives should be avoided in elderly patients with severe peripheral arterial disease as they may cause peripheral ischaemia. 'Drug holidays', which involve discontinuation of drugs, for example, for 2 days per week, may reduce the incidence of adverse effects of antiparkinsonian drugs, but their role is questionable.

Stroke

Stroke is the third most common cause of death and the most common cause of adult disability in the UK. About 110,000 people in England and Wales have their first stroke each year and about 30,000 people go on to have further strokes (National Collaborating Centre for Chronic Conditions, 2008). The incidence of stroke increases by 100-fold from the fourth to the ninth decade. About 85% of strokes are ischaemic and 15% are due to haemorrhages.

Treatment of acute stroke

Thrombolytic agents. The National Institute of Neurological Disorders and Stroke (1995) in the United States showed that, compared with placebo, thrombolysis with tissue plasminogen activator (rt-PA) within 3 h of onset of ischaemic stroke improved clinical outcome at 3 months despite increased incidence (6%) of symptomatic intracranial bleeding. Several studies have since confirmed the efficacy of intravenous rt-PA, administered within 3 h and up to 4.5 h, in acute ischaemic stroke. The odds ratio for improved outcome at 3 months, however, decreases from 2.5, if treatment is given between 0 and 90 min, to 1.3 between 181 and 270 min. A pooled analysis of the major randomised placebo-controlled trials of rt-PA (alteplase) for acute stroke showed large parenchymal haemorrhage in 5.2% of 1850 patients assigned to alteplase and 1.0% of 1820 controls, with no clear relation to onset of stroke to time of treatment (OTT). Adjusted odds of mortality increased with OTT (from 0.78 for 0–90 min to 1.22 for 181–270 min; Lees et al., 2010). Most of the clinical trials with rt-PA have excluded patients over 80 years of age. However, analysis of data from studies which have included patients over the age of 80 years, indicates that thrombolysis is effective in this age group but may be associated with a higher risk of bleeding. The currently ongoing International Stroke Trial 3 is specifically investigating the safety and efficacy of rt-PA in patients aged 80 years or more.

Antiplatelet therapy. Aspirin in doses of 150–300 mg commenced within 48 h of onset of ischaemic stroke has been shown to reduce the relative risk of death or dependency by 2.7% up to 6 months after the event in two large studies (Chen et al., 2000).

Anticoagulation. Use of intravenous unfractionated heparin and low molecular weight heparin have not been shown to be beneficial and are associated with increased risk of intracranial haemorrhage.

Neuroprotective agents. A large number of neuroprotective agents have been used for treatment of acute ischaemic stroke but none have been shown to have long-term beneficial effects.

Secondary prevention

Aspirin in doses of 75–1500 mg/day reduces the risk of stroke recurrence by about 23% as compared with placebo. This is likely to be due to its antiplatelet effect. Clopidogrel has been shown to reduce the relative risk for stroke recurrence by 8% compared with aspirin. When compared with aspirin alone, the combination of aspirin (75 mg daily) plus extended-release dipyridamole (200 mg twice daily) has been reported to reduce the relative risk by 20–23%. Aspirin plus extended-release dipyridamole has not been shown to be superior to clopidogrel alone in preventing recurrent stroke (Sacco et al., 2008). Clopidogrel plus aspirin (75 mg each daily) compared with aspirin alone is associated with an absolute increase in the risk for life-threatening bleeding by 1.3%, and therefore this combination is not recommended for secondary stroke prevention (Diener et al., 2004).

In patients with atrial fibrillation who have had a previous stroke or transient ischaemic attack, anticoagulation with warfarin (INR 1.5–2.7) has been shown to be significantly better than aspirin for secondary prevention (Hart et al., 2007). Anticoagulation has not been shown to be effective for secondary prevention in patients with sinus rhythm. Dabigatran, an oral direct thrombin inhibitor, at a dose of 110 mg twice daily is associated with similar rates of stroke and systemic embolism but lower rates of major haemorrhage. At a dose of 150 mg twice daily, it is associated with lower rates of stroke and systemic embolism but similar rates of major haemorrhage compared with warfarin (Connolly et al., 2009). Unlike warfarin, this drug does not require routine monitoring of anticoagulation. Two orally administered Factor Xa inhibitors, apixaban and rivaroxaban, are currently under investigation for stroke prevention in atrial fibrillation.

Adequate control of hypertension, diabetes, hyperlipidaemia, stopping smoking and reducing alcohol consumption are also important in secondary stroke prevention.

Primary prevention

A number of randomised controlled trials have shown that anticoagulation with warfarin compared with placebo reduces the risk of stroke in patients with atrial fibrillation (Hart et al., 2007). Control of risk factors such as hypertension, hyperlipidaemia, diabetes, and smoking is likely to play an important role in primary prevention.

Osteoporosis

Osteoporosis is a progressive disease characterised by low bone mass and micro-architectural deterioration of bone tissue resulting in increased bone fragility and susceptibility to fracture. It is an important cause of morbidity in postmenopausal women. The most important complication of osteoporosis is fracture of the hip. Fractures of wrist, vertebrae and humerus also occur. Increasing age is associated with higher risk of fractures, which occur mostly in those aged over 75 years. In the UK, over 200,000 fractures occur each year, costing the NHS £1.8 billion per year, of which 87% is spent on hip fractures (Poole and Compston, 2006).

Prevention

As complications of osteoporosis have enormous economic implications, preventive measures are extremely important. Regular exercise has been shown to halve the risk of hip fractures. Stopping smoking before the menopause reduces the risk of hip fractures by 25%.

Treatment

Vitamin D and calcium. Vitamin D deficiency is common in elderly people. Treatment for 12–18 months with 800 IU of vitamin D plus 1.2 g of calcium given daily has been shown to reduce hip and non-vertebral fractures in elderly women (mean age 84 years) living in sheltered accommodation. It is not known whether vitamin D supplementation alone reduces hip fractures. Calcium supplementation on its own does not reduce fracture incidence and is no longer recommended for treatment of osteoporosis.

Calcitriol and alfacalcidol. Calcitriol (1,25-dihydroxyvitamin D), the active metabolite of vitamin D, and alfacalcidol, a synthetic analogue of calcitriol, reduce bone loss and have been shown to reduce vertebral fractures, but not consistently. Serum calcium should be monitored regularly in patients receiving these drugs.

Bisphosphonates. Bisphosphonates, synthetic analogues of pyrophosphate, bind strongly to the bone surface and inhibit bone resorption. Currently, three oral bisphosphonates are available for the treatment of osteoporosis: alendronate, etidronate and risedronate. Alendronate can be given either daily (10 mg) or weekly (70 mg) with equal efficacy. It is effective in reducing vertebral, wrist and hip fractures by about 50%. Etidronate is given cyclically with calcium supplements to reduce the risk of bone mineralisation defects. It reduces the risk of vertebral fractures by 50% in postmenopausal women. There is no evidence to support its effectiveness in preventing hip fractures. Risedronate reduces vertebral fractures by 41% and non-vertebral fractures by 39%. It has been shown to significantly reduce the risk of hip fractures in postmenopausal women. Alendronate and risedronate are currently used as first-line drugs in older women with osteoporosis.

Intravenous ibandronate, given at a dose of 3 mg once every 3 months, can be used for treatment of postmenopausal osteoporosis. It can also be given orally at a dose of 150 mg once monthly.

All bisphosphonates cause gastro-intestinal side effects. Alendronate and risedronate are associated with severe oesophageal reactions including oesophageal stricture. Patients should not take these tablets at bed-time and should be advised to stay upright for at least 30 min after taking them. They should avoid food for at least 2 h before and after taking etidronate. Alendronate and risedronate should be taken 30 min before the first food or drink of the day. Bisphosphonates should be avoided in patients with renal impairment.

Strontium ranelate, which both increases bone formation and reduces bone resorption, reduces vertebral and non-vertebral (including hip) fractures in postmenopausal women with osteoporosis. It is well tolerated. It can be used in those who are unable to tolerate alendronate or risedronate. It should be avoided in patients with severe renal disease (creatinine clearance below 30 mL/min). It can be used with caution in patients at increased risk of venous thromboembolism and those with phenylketonuria.

Hormone replacement therapy (HRT). Oestrogens increase bone formation and reduce bone resorption. They also increase calcium absorption and decrease renal calcium loss. HRT, if started soon after the menopause, is effective in preventing vertebral fractures but has to be continued lifelong if protection against fractures is to be maintained. It is associated with increased risk of endometrial cancer, breast cancer and venous thromboembolism. One study has shown

that HRT may increase the risk of deaths due to myocardial disease in elderly women with pre-existing ischaemic heart disease. It should be avoided in older patients.

Raloxifene. Raloxifene, an oral selective oestrogen receptor modulator (SERM) that has oestrogenic actions on bone and anti-oestrogenic actions on the uterus and breast. It reduces the risk of vertebral fractures, but not those at other sites. Adverse effects include hot flushes, leg cramps, and risk of venous thromboembolism. It also protects against breast cancer. Its use is restricted, as a second-line drug, to younger postmenopausal women with vertebral osteoporosis.

Parathyroid hormone peptides. Teriparatide is the recombinant portion of human parathyroid hormone, amino acid sequence 1–34, of the complete molecule (which has 84 amino acids). It reduces vertebral and non-vertebral fractures in postmenopausal women. It does not reduce hip fractures. It is given subcutaneously at a dose of 20 µcg daily. The recombinant (full 1–84 amino acid sequence) parathyroid hormone peptide (Preotact®) can also be used at a dose of 100 µcg daily. It has similar efficacy as teriparatide. Both these drugs are expensive and teriparatide is associated with an increased risk of osteosarcoma in animal studies.

Calcitonin. Calcitonin inhibits osteoclasts and decreases the rate of bone resorption, reduces bone blood flow and may have central analgesic actions. It is effective in all age groups in preventing vertebral bone loss. It is costly and has to be given parenterally or intranasally. It should not be given for more than 3–6 months at a time to avoid its inhibitory effects on bone resorption and formation, which usually disappear after 2–4 weeks. Antibodies do develop against calcitonin, but they do not affect its efficacy. Calcitonin is useful in treating acute pain associated with osteoporotic vertebral fractures.

Arthritis

Osteoarthrosis, gout, pseudogout, rheumatoid arthritis and septic arthritis are the important joint diseases in the elderly. Treatment of these conditions is similar to that in the young. If possible, NSAIDs should be avoided in patients with osteoarthrosis. Total hip and knee replacements should be considered in patients with severe arthritis affecting these joints.

Hypertension

Hypertension is an important risk factor for cardiovascular and cerebrovascular disease in the elderly. The incidence of myocardial infarction is 2.5 times higher, and that of cerebrovascular accidents twice as high in elderly hypertensive patients compared with non-hypertensive subjects. Elevated systolic blood pressure is the single most important risk factor for cardiovascular disease and more predictive of stroke than diastolic blood pressure.

Blood pressure lowering has been shown to be beneficial in those patients below and above the age of 65 years with no substantial variation in reduction in major vascular events with different drug classes (Blood Pressure Lowering Treatment Trialists' Collaboration, 2008). There is evidence that treatment of both systolic and diastolic blood pressure in the elderly is beneficial. One large study has shown reductions in cardiovascular events, and mortality associated with cerebrovascular accidents in treated elderly patients with hypertension (Amery et al., 1986). The treatment did not reduce the total mortality significantly. Another study (SHEP, 1991), which used low-dose chlortalidone to treat isolated systolic hypertension (systolic blood pressure 160 mmHg or more with diastolic blood pressure less than 95 mmHg), showed a 36% reduction in the incidence of stroke, with a 5-year benefit of 30 events per 1000 patients. It also showed a reduction in the incidence of major cardiovascular events with a 5-year absolute benefit of 55 events per 1000 patients. In addition, this study reported that antihypertensive therapy was beneficial even in patients over the age of 80 years. There is increasing evidence that antihypertensive therapy in patients over 80 years of age is beneficial. Subgroup meta-analysis of seven randomised controlled trials, which included 1670 patients over 80 years, showed that antihypertensive therapy for about 3.5 years reduces the risk of heart failure by 39%, strokes by 34% and major cardiovascular events by 22% (Gueyffier, 1999). In one placebo-controlled study which included 3845 patients who were 80 years of age or older and had a sustained systolic blood pressure of 160 mmHg or more, treatment with the diuretic indapamide (sustained release, 1.5 mg) plus perindopril (2 or 4 mg) to achieve the target blood pressure of 150/80 mmHg resulted in a 30% reduction in the rate of fatal or non-fatal stroke, a 39% reduction in the rate of death from stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes and a 64% reduction in the rate of heart failure (Beckett et al., 2008).

Treatment of hypertension

Non-pharmacological. In patients with asymptomatic mild hypertension, non-pharmacological treatment is the method of choice. Weight reduction to within 15% of desirable weight, restriction of salt intake to 4–6 g/day, regular aerobic exercise such as walking, restriction of ethanol consumption and stopping smoking are the recommended modes of therapy.

Pharmacological

Thiazide diuretics. Thiazides lower peripheral resistance and do not significantly affect cardiac output or renal blood flow. They are effective, cheap, well tolerated and have also been shown to reduce the risk of hip fracture in elderly women by 30%. They can be used in combination with other antihypertensive drugs. Adverse effects include mild elevation of creatinine, glucose, uric acid and serum cholesterol levels as well as hypokalaemia. They should be used in low doses, as higher doses only increase the incidence of adverse effects without increasing their efficacy.

β-Adrenoceptor blockers. Although theoretically the β-blockers are expected to be less effective in the elderly, they have been shown to be as effective as diuretics in clinical

studies. Water-soluble β-blockers such as atenolol may cause fewer adverse effects in the elderly.

Calcium antagonists. Calcium antagonists act as vasodilators. Verapamil and, to some extent, diltiazem decrease cardiac output. These drugs do not have a significant effect on lipids or the central nervous system. They may be more effective in the elderly, particularly in the treatment of isolated systolic hypertension. Adverse effects include headache, oedema and postural hypotension. Verapamil may cause conduction disturbances and decrease cardiac output. The use of short-acting dihydropyridine calcium antagonists, for example nifedipine, is controversial. Some studies indicate adverse outcomes with these agents, particularly in those patients with angina or myocardial infarction.

ACE inhibitors and angiotensin receptor blockers (ARBs): ACE inhibitors and ARBs used for treatment of hypertension are discussed elsewhere (see chapter 19). These drugs should be used with care in the elderly, who are more likely to have underlying atherosclerotic renovascular disease that could result in renal failure. Excessive hypotension is also more likely to occur in the elderly.

Myocardial infarction

The diagnosis of myocardial infarction in the elderly may be difficult in some patients because of an atypical presentation (Bayer et al., 1986). In the majority of patients, chest pain and dyspnoea are the common presenting symptoms. Confusion may be a presenting factor in up to 20% of patients over 85 years of age. The diagnosis is made on the basis of history, serial electrocardiograms and cardiac enzyme estimations.

The principles of management of myocardial infarction in the elderly are similar to those in the young. Thrombolytic therapy has been shown to be safe and effective in elderly patients.

Cardiac failure

In addition to the typical features of cardiac failure, that is, exertional dyspnoea, oedema, orthopnoea and paroxysmal nocturnal dyspnoea (PND), elderly patients may present with atypical symptoms. These include confusion due to poor cerebral circulation, vomiting and abdominal pain due to gastro-intestinal and hepatic congestion, or insomnia due to PND. Dyspnoea may not be a predominant symptom in an elderly patient with arthritis and immobility. Treatment of cardiac failure depends on the underlying cause and is similar to that in the young. Diuretics, ACE inhibitors, β-blockers and digoxin are the important drugs used in the treatment of cardiac failure in the elderly.

Leg ulcers

Leg ulcers are common in the elderly. They are mainly of two types: venous or ischaemic. Other causes of leg ulcers are blood diseases, trauma, malignancy and infections (Cornwall et al., 1986), but these are less common in the elderly. Venous ulcers occur in patients with varicose veins who have valvular incompetence in deep veins due to venous hypertension. They are usually located near the medial malleolus and are associated with varicose eczema and oedema. These ulcers are painless unless there is gross oedema or infection. Ischaemic ulcers, on the other hand, are due to poor peripheral circulation, and occur on the toes, heels, foot and lateral aspect of the leg. They are painful and are associated with signs of lower limb ischaemia, such as absent pulse or cold lower limb. There may be a history of smoking, diabetes or hypertension.

Venous ulcers respond well to treatment, and over 75% heal within 3 months. Elevation of the lower limbs, exercise, compression bandage, local antiseptic creams when there is evidence of infection, with or without steroid cream, are usually effective. There is no evidence of benefit from the use of oral zinc sulphate in patients with chronic leg ulcers. Dressings impregnated with silver have not been shown to be better than simple low-adherent dressings for the healing of venous leg ulcers. Use of 5% Eutectic Mixture of Local Anaesthetics (EMLA): lidocaine–prilocaine cream results in statistically significant reduction in debridement pain scores but it appears to have no impact on wound healing. Ibuprofen dressings have not been shown to offer pain relief (Briggs et al., 2010). Antiseptics should not be used when there is granulation tissue. Topical streptokinase may be useful to remove the slough on ulcers. Gell colloid occlusive dressings may also be useful in treating chronic ulcers. Skin grafting may be necessary for large ulcers. Ischaemic ulcers do not respond well to medical treatment, and the patients should be assessed by vascular surgeons.

Urinary incontinence

Urinary incontinence in the elderly may be of three main types:

Stress incontinence: due to urethral sphincter incompetence. It occurs almost exclusively in women and is associated with weakening of pelvic musculature. Involuntary loss of small amounts of urine occurs on performing activities which increase intra-abdominal pressure, for example, coughing, sneezing, bending, lifting, etc. It does not cause significant nocturnal symptoms.

Overlow incontinence: constant involuntary loss of urine in small amounts. Prostatic hypertrophy is a common cause and is often associated with symptoms of poor stream and incomplete emptying. Increased frequency of micturition at night is often a feature. Use of anticholinergic drugs and diabetic autonomic neuropathy are other causes.

Detrusor instability: causes urge incontinence where a strong desire to pass urine is followed by involuntary loss of large amounts of urine either during the day or night. It is often associated with neurological lesions or urinary outflow obstruction, for example, prostatic hypertrophy, but in many cases the cause is unknown.

Stress incontinence is not amenable to drug therapy. In patients with prostatic hypertrophy α_1-blockers such as prazosin, indoramin, alfuzosin, terazosin, and tamsulosin

have all been shown to increase peak urine flow rate and improve symptoms in about 60% of patients. They reduce outflow obstruction by blocking α_1-receptors and thereby relaxing prostate smooth muscle. Postural hypotension is an important adverse effect and occurs in between 2% and 5% of patients.

5α-Reductase converts testerone to dihydrotesterone (DHT) which plays an important role in the growth of prostate. The 5α-reductase inhibitor finasteride reduces the prostate volume by 20% and improves peak urine flow rate. The clinical effects, however, might not become apparent until after 3–6 months of treatment. Main adverse effects are reductions in libido and erectile dysfunction in 3–5% of patients.

Several antimuscarinic drugs including darifenacin, oral and transdermal oxybutynin, modified-release propiverine, solifenacin, and modified-release tolterodine have been licensed for overactive bladder syndrome. All these drugs are similar in efficacy and cause antimuscarinic side effects such as dry mouth, blurred vision and constipation. Immediate-release oxybutynin is the least expensive drug and is more likely to cause adverse effects. Transdermal and modified release preparations are better tolerated, but are more expensive (Anon, 2007).

Constipation

The age-related decline in gastro-intestinal motility and treatment with drugs which decrease gastro-intestinal motility predispose the elderly to constipation. Decreased mobility, wasting of pelvic muscles and a low intake of solids and liquids are other contributory factors. Faecal impaction may occur with severe constipation, which in turn may cause subacute intestinal obstruction, abdominal pain, spurious diarrhoea and faecal incontinence. Adequate intake of dietary fibre, regular bowel habit and use of bulking agents such as bran or ispaghula husk may help to prevent constipation. When constipation is associated with a loaded rectum, a stimulant laxative such as senna or bisacodyl may be given. Frail, ill elderly patients with a full rectum may have atonic bowels that will not respond to bulking agents or softening agents, and in such cases a stimulant is more effective. A stool-softening agent such as docusate sodium is effective when stools are hard and dry. For severe faecal impaction a phosphate enema may be needed. Long-term use of stimulant laxatives may lead to abuse and atonic bowel musculature.

Gastro-intestinal ulceration and bleeding

Gastro-intestinal bleeding associated with peptic ulcer is less well tolerated by the elderly. The clinical presentation may sometimes be atypical with, for example, patients presenting with confusion. *Helicobacter pylori* infection is common and its treatment is similar to that in younger patients. NSAIDs are more likely to cause gastroduodenal ulceration and bleeding in the elderly (Griffin et al., 1988).

Principles and goals of drug therapy in the elderly

A thorough knowledge of the pharmacokinetic and pharmacodynamic factors discussed is essential for optimal drug therapy in the elderly. In addition, some general principles based on common sense, if followed, may result in even better use of drugs in the elderly.

Avoid unnecessary drug therapy

Before commencing drug therapy it is important to ask the following questions:

- Is it really necessary?
- Is there an alternative method of treatment?

In patients with mild hypertension, non-drug therapies which are of proven efficacy should be considered in the first instance. Similarly, unnecessary use of hypnotics should be avoided. Simple measures such as emptying the bladder before going to bed to avoid having to get up, avoidance of stimulant drugs in the evenings or night, or moving the patient to a dark, quiet room may be all that is needed.

Effect of treatment on quality of life

The aim of treatment in elderly patients is not just to prolong life but also to improve the quality of life. To achieve this, the correct choice of treatment is essential. In a 70-year-old lady with severe osteoarthrosis of the hip, for example, total hip replacement is the treatment of choice rather than prescribing NSAIDs with all their attendant adverse effects.

Treat the cause rather than the symptom

Symptomatic treatment without specific diagnosis is not only bad practice but can also be potentially dangerous. A patient presenting with 'indigestion' may in fact be suffering from angina, and therefore treatment with proton pump inhibitors or antacids is clearly inappropriate. When a patient presents with a symptom every attempt should be made to establish the cause of the symptom and specific treatment, if available, should then be given.

Drug history

A drug history should be obtained in all elderly patients. This will ensure the patient is not prescribed a drug or drugs to which they may be allergic, or the same drug or group of drugs to which they have previously not responded. It will help to avoid potentially serious drug interactions.

Concomitant medical illness

Concurrent medical disorders must always be taken into account. Cardiac failure, renal impairment and hepatic dysfunction are particularly common in the elderly, and may increase the risk of adverse effects of drugs.

Choosing the drug

Once it is decided that a patient requires drug therapy, it is important to choose the drug likely to be the most efficacious and least likely to produce adverse effects. It is also necessary to take into consideration coexisting medical conditions. For example, it is inappropriate to commence diuretic therapy to treat mild hypertension in an elderly male with prostatic hypertrophy.

Dose titration

In general, elderly patients require relatively smaller doses of all drugs compared with young adults. It is recognised that the majority of adverse drug reactions in the elderly are dose related and potentially preventable. It is, therefore, rational to start with the smallest possible dose of a given drug in the least number of doses and then gradually increase both, if necessary. Dose titration should obviously take into consideration age-related pharmacokinetic and pharmacodynamic alterations that may affect the response to the chosen drug.

Choosing the right dosage form

Most elderly patients find it easy to swallow syrups or suspensions or effervescent tablets rather than large tablets or capsules.

Packaging and labelling

Many elderly patients with arthritis find it difficult to open child-resistant containers and blister packs. Medicines should be dispensed in easy-to-open containers that are clearly labelled using large print.

Good record keeping

Information about a patient's current and previous drug therapy, alcohol consumption, smoking and driving habits may help in choosing appropriate drug therapy and when the treatment needs to be altered. It will help to reduce costly duplications and will also identify and help to avoid dangerous drug interactions.

Regular supervision and review of treatment

A UK survey showed that 59% of prescriptions to the elderly had been given for more than 2 years, 32% for more than 5 years and 16% for more than 10 years. Of all prescriptions given to the elderly, 88% were repeat prescriptions; 40% had not been discussed with the doctor for at least 6 months, especially prescriptions for hypnotics and anxiolytics. It also showed that 31% of prescriptions were considered pharmacologically questionable, and 4% showed duplication of drugs. It is obvious that there is a need for regular and critical review of all prescriptions, especially when long-term therapy is required.

Adverse drug reactions (ADRs)

It is recognised that ADRs occur more frequently in the elderly. A multicentre study in the UK in 1980 showed that ADRs were the only cause of admission in 2.8% of 1998 admissions to 42 units of geriatric medicine. It also showed that ADRs were contributory to a further 7.7% of admissions. On the basis of this study it can be estimated that up to 15,000 geriatric admissions per annum in the UK are at least partly due to an ADR. Obviously, this has enormous economic implications.

The elderly are more susceptible to ADRs for a number of reasons. They are usually on multiple drugs, which in itself can account for the increased incidence of ADRs. It is, however, recognised that ADRs tend to be more severe in the elderly, and gastro-intestinal and haematological ADRs are more common than would be expected from prescribing figures alone. Age-related pharmacokinetic and pharmacodynamic alterations and impaired homeostatic mechanisms are the other factors which predispose the elderly to ADRs, by making them more sensitive to the pharmacological effects of the drugs. Not surprisingly, up to 80% of ADRs in the elderly are dose-dependent and therefore predictable.

Adherence

Although it is commonly believed that the elderly are poor compliers with their drug therapy, there is no clear evidence to support this. Studies in Northern Ireland and continental Europe have shown that the elderly are as adherent with their drug therapy as the young, provided that they do not have confounding disease. Cognitive impairment, which is common in old age, multiple drug therapy and complicated drug regimens may impair adherence in the elderly. Poor adherence may result in treatment failure. The degree of adherence required varies depending on the disease being treated. For treatment of a simple urinary tract infection, a single dose of an antibiotic may be all that is required, and therefore compliance is not important. On the other hand, adherence of 90% or more is required for successful treatment of epilepsy or difficult hypertension. Various methods have been used to improve adherence. These include prescription diaries, special packaging, training by pharmacists and counselling.

Conclusion

The number of elderly patients, especially those aged over 75 years, is steadily increasing, and they are accounting for an ever-increasing proportion of health care expenditure in the West. Understanding age-related changes in pharmacodynamic factors, avoiding polypharmacy and regular and critical review of all drug treatment will help in the rationalisation of drug prescribing, reduction in drug-related morbidity and also the cost of drug therapy for this important subgroup of patients.

Case studies

Case 11.1

An 80-year-old woman presented to an out-patient clinic with a history of severe giddiness and a few episodes of blackouts. She was being treated for angina and hypertension. She had been on bendroflumethiazide 2.5 mg once daily, and slow-release isosorbide mononitrate 60 mg once daily for a few years. Her general practitioner had recently commenced nifedipine SR 20 mg twice daily for poorly controlled hypertension. On examination her blood pressure was 120/70 mmHg while supine and 90/60 mmHg on standing up.

Question

What is the underlying problem in this patient, and could it be caused by any of the medications that the patient is taking?

Answer

This patient obviously has significant postural hypotension. All her drugs have the potential to produce postural hypotension, and when used together they may produce symptomatic postural hypotension.

It is important to recognise that some drugs such as nifedipine and nitrates have impaired first-pass metabolism in the elderly and that their clinical effects are enhanced. In addition, orthostatic circulatory responses are also impaired in the elderly. The need for antihypertensive drugs should be carefully assessed in all elderly patients, and, if therapy is indicated, the smallest dose of drug should be commenced and increased gradually. Patients should also be told to avoid sudden changes of posture.

Case 11.2

An 85-year-old man was admitted to hospital with anorexia, nausea and vomiting. He was known to have atrial fibrillation, congestive cardiac failure and chronic renal impairment. He was on digoxin 250 µcg once daily and furosemide 80 mg twice daily.

His serum biochemistry revealed the following (normal range in parentheses):

Potassium	**4.5 mmol/L**	**(3.5–5)**
Urea	**40 mmol/L**	**(3.0–6.5)**
Creatinine	**600 µmol/L**	**(50–120)**
Digoxin	**3.5 µcg/L**	**(1–2)**

Question

What are the likely causes of medical problems in this patient and how should the drug therapy be altered?

Answer

The patient's biochemical results confirm the presence of renal impairment and digoxin toxicity. The renal impairment could be related to the relatively high dose of furosemide which needs to be reduced. As digoxin is predominantly excreted through the kidneys, the dose should be reduced in severe renal impairment. In such situations, digitoxin, which is predominantly metabolised in the liver, can be used instead of digoxin.

Case 11.3

An 80-year-old woman with a previous history of hypothyroidism presented with a history of abdominal pain and vomiting. She had not moved her bowels for the previous 7 days. Two weeks earlier her general practitioner had prescribed a combination of paracetamol and codeine to control pain in her osteoarthritic hips.

Question

What are the likely underlying causes of this patient's bowel dysfunction?

Answer

This patient developed severe constipation after taking a codeine-containing analgesic. Ageing is associated with decreased gastro-intestinal motility. Hypothyroidism, which is common in the elderly, is also associated with reduced gastro-intestinal motility. Whenever possible, drugs that are known to reduce gastro-intestinal motility should be avoided in the elderly.

Case 11.4

A 75-year-old lady who suffered from osteoarthritis of hip and knee joints presented with a history of passing black stools. Her drug therapy included diclofenac 50 mg three times daily and paracetamol 1 g as required.

Question

What is the likely cause of this patient's symptoms?

Answer

The likely cause is upper gastro-intestinal bleeding due to diclofenac, which is an NSAID. Elderly people are more prone to develop ulceration in stomach and duodenum with NSAIDs compared with young patients.

Case 11.5

A 70-year-old man was found by his general practitioner to have hypertension and was commenced on lisinopril 5 mg once a day. He had a previous history of peripheral vascular disease for which he had required angioplasty. Two weeks after commencing antihypertensive treatment, he presented with lack of appetite, nausea and decreased urine output.

Question

What do you think has happened and is the most likely underlying problem?

Answer

The patient is probably developing renal failure. With a previous history of peripheral vascular disease, he is likely to have bilateral renal artery stenosis. ACE inhibitors can cause renal failure in the presence of bilateral renal stenosis by reducing blood supply to the kidneys.

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