15

Individualization and Optimization of Drug Dosing Regimens

Drug therapy is so routine that even physicians and pharmacists sometimes take for granted the unusual complexity of the process. The scheme in Figure 15–1 shows some of the steps involved in the initiation and management of drug therapy.[1] The major tasks are defining the therapeutic objective, selecting the drug and its dosage regimen, and evaluating whether or not the objective has been met. Selecting a drug is an exercise in therapeutics, but selecting the dosage regimen is a quantitative task that usually requires an understanding of clinical pharmacokinetics. The evaluation of how well the therapeutic objective has been achieved and the decision to modify the dosage regimen or turn to another drug also requires the knowledge base of clinical pharmacology and clinical pharmacokinetics.

INDIVIDUALIZING DOSAGE REGIMENS

Not so long ago essentially all patients needing a certain drug were prescribed the same dose. Pharmacodynamic and pharmacokinetic variability had no place in the initiation of drug therapy. During 1970 to 1972, Koch-Weser surveyed phenytoin dosages prescribed for seizure prevention to 200 ambulatory patients and found that 92% of the patients received the usual dose of 300 mg/day.[2] This observation is remarkable because phenytoin is the quintessential example of a drug with substantial interpatient variability in clinical response.

Today, a clinician initiating a dosage regimen considers the patient's age, size, disease status, and concomitant drug therapy. It is now common to find higher than usual mg/kg doses of theophylline prescribed for children or smokers and lower than usual dosages prescribed for patients w
tive heart failure (CHF). Dosages of
otics, digoxin, lithium, and other dru
tinely reduced for patients with impa
function. More conservative dosages of hypnotics, antianxiety drugs, and other psychotropic agents are prescribed for the elderly. The information on drug characteristics in different patient populations is now being applied to the individual patient.

OPTIMIZING DOSAGE REGIMENS

Incorporating the patient's characteristics in the process of initiating a drug dosage regimen is an important step toward optimization of drug therapy, but it does not guarantee the success of the therapy. We still need to evaluate the outcome of the treatment and we still find in some cases that the therapeutic objective has not been achieved. There are many reasons for failure, including the need for larger or smaller dosages of the drug. This is not surprising because few schemes to individualize the initial dosage regimen take into account the pharmacokinetics of the drug in the individual patient or the individual's responsiveness to the drug. Individualization of the initial dosing regimen is usually based on population rather than individual data. To the extent that the patient deviates from the population average, his response will deviate from the therapeutic objective.

Traditionally, the management of drug therapy has been accomplished by monitoring the incidence and intensity of both desired therapeutic effects and undesired adverse effects; an inadequate therapeutic response calls for a higher dosage, drug-related toxicity calls for a lower dosage. The patient with

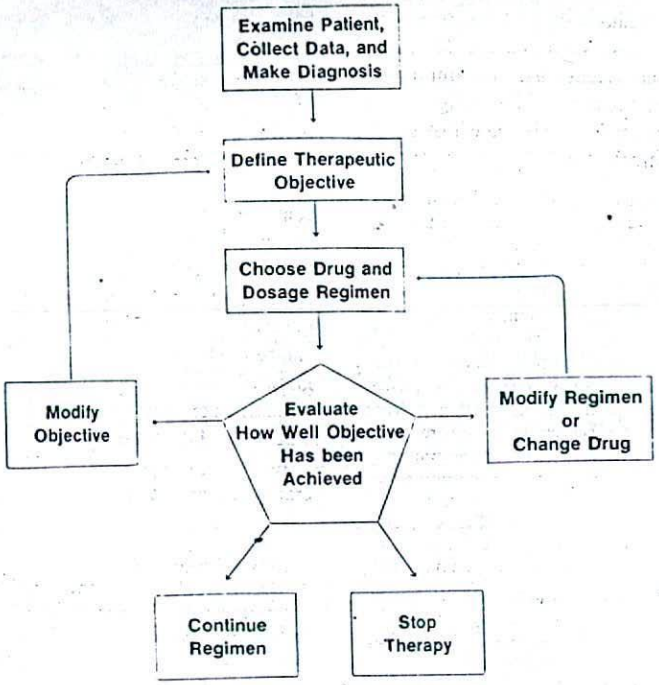

Fig. 15–1. Steps in the initiation and management of drug therapy. (From Rowland, M., and Tozer, T.N.[1])

rheumatoid arthritis who shows inadequate reduction of inflammation and continued pain in response to treatment with a nonsteroidal anti-inflammatory drug and the patient with asthma who experiences insufficient bronchodilation in response to treatment with theophylline probably need higher dosages. But what do we mean by inadequate and insufficient? The words are imprecise because our ability to measure therapeutic outcome is usually imprecise. Individual management of drug dosage regimens based on clinical efficacy requires an inordinate degree of skill and an unreasonable share of the physician's time and attention.

Our ability to measure excessive drug dosage is also limited. At one time we thought that tinnitus during salicylate therapy and nausea during theophylline therapy were harbingers of drug toxicity. The emergence of these signs would permit us to reduce drug dosage before the onset of more serious toxicity. Today, we recognize that some patients do not hear or discern the ringing in the ears characteristic of high serum concentrations of salicylate and can develop life-threatening metabolic acidosis. Fatal theophylline-induced convulsive seizures have been observed in patients who displayed no signs of nausea.

The problems illustrated by theophylline and salicylate are common; they suggest that traditional management of drug therapy based on clinical outcome can rarely be applied in its purest form. The closest we come to it is in the management of oral anticoagulant, oral antidiabetic, or uricosuric therapy. Although we do not directly assess the therapeutic objectives in these cases, we do substitute and closely monitor a laboratory test (i.e., prothrombin time, urine glucose, or uric acid levels) that is closely related to the objective. There is a continual and intensive search for biochemical correlates of drug effects, but this desirable alternative is available for few drugs.

Titrating a drug dosing regimen to a target concentration range in blood or plasma is yet another strategy. It is not as precise as titrating to a biochemical end point, but when combined with an assessment of clinical outcome it is often superior to clinical evaluation alone.

During the past 30 years, plasma concentrations of drugs have been measured during their therapeutic use. This has been made possible by the

development of methods of analysis (e.g., gas chromatography, mass spectrometry, high-pressure liquid chromatography, and radioimmunoassay) that allow determination of low drug concentrations. A review article on this subject offers the following comments:[3]

> Measurement of serum levels of a drug become useful guides for dosage adjustments only when the therapeutically effective range of serum concentrations has been defined by careful clinical studies. At present, this has been accomplished for few important drugs. Compared to the large individual variations in the optimal dosages of these drugs, the width of their therapeutic serum concentration ranges is relatively narrow. Concentrations of these drugs below the therapeutic range can exert beneficial effects but are inadequate in most patients. Within the therapeutic range the intensity of the desired effect of the drug increases with its serum concentration. In occasional patients, high therapeutic concentrations may have minor toxic actions. As serum concentrations rise above the therapeutic range, the frequency and severity of toxic effects increase progressively. Some patients can tolerate serum concentrations above the usual therapeutic levels, and a few may even require them for a fully satisfactory response. Thus, some overlap between therapeutic and toxic serum concentrations is the rule, and it is considerable for certain drugs, such as the digitalis glycosides. Whenever concentrations above the usual therapeutic range are produced for therapeutic purposes, patients must be closely monitored for the appearance of serious toxicity.

Evans[4] has pointed out that the idea of a therapeutic range for serum concentrations of drugs is frequently misunderstood. Some assume that the therapeutic range for most drugs has been well-defined from carefully controlled trials and that drug concentrations in the therapeutic range will result in the desired clinical response with no adverse effects. Evans presents a more precise definition of therapeutic range as "a range of drug concentrations within which the probability of the desired clinical response is relatively high and the probability of unacceptable toxicity is relatively low."

Drug level determinations cannot substitute for clinical judgment and must always be interpreted in the context of available clinical data. By reducing the number of unknown variables, however, the availability of such data permits the physician to apply his clinical skills to the maximum by focusing more directly on the disease process and on the physiologic status of the patient.

The experience of the past decade with determination of serum drug levels in the clinical setting has been extensive and exciting. New journals have been devoted to therapeutic drug concentration monitoring[5] and clinical pharmacokinetics.[6] Several books on the subject are available.[4,7,8] Many of the reports in the clinical pharmacology and pharmacy literature today are concerned with applications of pharmacokinetics. As is true of many sound concepts, however, therapeutic drug concentration monitoring for optimization of drug therapy must be placed in perspective.

Koch-Weser has pointed out that routine determination of serum concentrations of all drugs is not the sine qua non of good patient care.[9] Drugs can be and have been used effectively without any knowledge of their concentrations in the body; determination of serum concentrations does not guarantee skillful drug therapy.

According to Richens and Warrington, the general indications for plasma drug level monitoring are as follows:[10]

> 1) When there is a wide interindividual variation in the rate of metabolism of the drug, leading to marked differences in steady-state plasma levels. This can be particularly important in children, in whom differences in body weight and metabolic rate are wide.
>
> 2) When saturation kinetics occur, causing a steep relationship between dose and plasma level within the therapeutic range (e.g., phenytoin).
>
> 3) When the therapeutic ratio of a drug is low; i.e., when therapeutic doses are close to toxic doses (e.g. aminoglycoside antibiotics).
>
> 4) When signs of toxicity are difficult to recognize clinically, or where signs of overdosage or underdosage are indistinguishable.
>
> 5) When gastrointestinal, hepatic or renal disease is present, causing disturbance of drug absorption, metabolism or excretion.
>
> 6) When patients are receiving multiple drug therapy with the attendant risk of drug interaction.
>
> 7) When there is doubt about the patient's reliability in taking his tablets.

An important illustration of the potential benefits of monitoring plasma drug levels is found in a report on digoxin toxicity from the Boston Collaborative Drug Surveillance Program.[11] Adverse reactions to digoxin in hospitalized medical patients were monitored for 2 years at 2 Boston hospitals. Dose-related adverse reactions were confirmed in 10% of 272 patients at 1 hospital but in only 4% of 291 patients at the other. The only important difference between these hospitals was that serum digoxin concentrations were measured in more patients receiving digoxin at the second hospital (40%) than at the first (12%). Mean digoxin levels were lower at the second hospital than at the first,

probably reflecting the use of serum digoxin concentration monitoring for therapeutic guidance. The authors conclude that the use of serum digoxin assays in clinical practice can decrease the frequency of adverse reactions to this drug.

CLINICAL EXPERIENCE WITH INDIVIDUALIZATION AND OPTIMIZATION BASED ON PLASMA DRUG LEVELS

There are few well-controlled prospective studies to show that individualization of initial drug dosing regimens and monitoring of plasma drug levels to optimize drug dosages result in better drug therapy. If this kind of evidence were a requirement, however, cardiac bypass surgery, liver transplants, and most other clinical procedures would not be available. In the absence of controlled, prospective studies, the value of individualization and optimization of certain drug therapies must be judged on clinical experience. The balance of this chapter concerns specific drugs for which individualization of dosage regimens and/or routine or selective monitoring of plasma concentrations have been found by some investigators to be helpful in guiding therapy and minimizing adverse effects.

Antiarrhythmic Drugs

Most antiarrhythmic agents have a narrow therapeutic window, requiring careful titration of dosage. Investigators first proposed the use of plasma level monitoring for antiarrhythmic drugs nearly 40 years ago by characterizing the relation between antiarrhythmic response and plasma concentrations of quinidine.[12] Since that pioneering work other investigators have sought a relationship between drug level and response for other antiarrhythmic drugs.[13]

In a recent review, Woosley[14] stated that "plasma concentration monitoring of antiarrhythmic agents is valuable, but it is often misused or overemphasized in therapeutic decision-making . . . For maximum value, there must be a reliable, accurate relation between the plasma drug concentration and drug action, a relation closer than that between dosage and drug action."

Procainamide. Procainamide is usually given orally for prophylaxis of arrhythmias. It has a short half-life (2.5 to 5.0 hr) and a narrow therapeutic concentration range. About 40 to 60% of a dose of procainamide is excreted in the urine. Oral and intravenous dosages of the drug must be reduced in patients with impaired renal function.

The clinical pharmacokinetics of procainamide and the use of serum procainamide levels as therapeutic guides have been reviewed.[15,16] The usually effective antiarrhythmic plasma procainamide concentrations are 4 to 8 μg/ml; in some patients, higher concentrations are more effective. Toxic manifestations are uncommon at plasma concentrations less than 12 μg/ml, but are seen often with concentrations more than 16 μg/ml.[17] Serious toxic effects include marked hypotension, disturbances in conduction, major active ventricular arrhythmias, and cardiac arrest.

Blood samples for monitoring plasma procainamide concentrations are taken when steady state is attained; this usually occurs within 24 hr of initiating oral therapy but may require up to 2 days in patients with little renal function or when a prolonged-release product is used. Typically, two blood samples are obtained during a steady-state dosing interval; one sample is collected at the end of a dosing interval and the other 2 hr later to approximate the peak drug concentration.

Therapeutic plasma levels of procainamide were established before it was known that N-acetylprocainamide (NAPA), a principal metabolite, could contribute to the therapeutic and toxic effects of procainamide. The relationship between plasma NAPA levels and antiarrhythmic activity has not been established. Some investigators have claimed that NAPA's activity is similar to that of procainamide at equal plasma concentrations; others have reported that higher levels of NAPA, on the order of 10–20 μg/ml, are needed to suppress arrhythmias.

Patients with poor renal function who are genetically rapid acetylators will have the highest ratios of NAPA to procainamide concentrations in plasma. These patients may show a good clinical response even when procainamide levels are below those usually associated with efficacy.[7]

Quinidine. Quinidine is useful for both prophylaxis and treatment of a variety of atrial and ventricular arrhythmias. It is usually administered orally but may be given by intramuscular or intravenous injection. About 60 to 80% of an intravenous dose of quinidine is metabolized in the liver; it has a half-life of about 6 to 7 hr. Maintenance dosages of quinidine may need to be reduced by one third to one half in patients with CHF.[18] When usual dosages of quinidine are given to patients on enzyme-inducing drugs, such as phenobarbital, phenytoin, or rifampin, low, subtherapeutic blood

levels of quinidine are likely to result. Higher than usual dosages of quinidine are required in these patients, but these dosages must be reduced if the enzyme-inducer is withdrawn. The clinical pharmacokinetics of quinidine has been reviewed by Ochs and associates.[19]

Confusion has existed concerning the therapeutic concentration range of quinidine. Quinidine concentrations that are determined with a nonspecific assay method will be higher than actual quinidine concentrations. With these older methods, the therapeutic range for quinidine is higher than the range determined with more specific methods. Quinidine concentrations of about 3 to 8 μg/ml are considered therapeutic when nonspecific assay methods are used.

As assay specificity for quinidine improves, therapeutic effects are associated with lower plasma concentrations. With a high performance liquid chromatography assay procedure or the EMIT method, both of which are in common use, antiarrhythmic effects are associated with serum quinidine levels of 2 to 5 μg/ml.[20]

The frequency of gastrointestinal disturbances increases with quinidine levels above 5 μg/ml; cardiovascular disturbances are a concern at concentrations exceeding 8 μg/ml. Cardiovascular toxicity of quinidine includes re-entrant arrhythmias that could lead to heart block. Several metabolites of quinidine have cardiovascular effects in laboratory animals, but their clinical significance is not known.

Woosley[14] observed that "restriction of dosages to maintain plasma levels below a predetermined limit is of value with drugs such as quinidine, which have variable clearance . . . However, careful dose titration and electrocardiographic monitoring are essential because plasma concentration monitoring is of only limited value in guiding therapy." Woosley believes that the most important role for plasma concentration monitoring is to ensure adequate dosing in those patients who rapidly clear quinidine.

Quinidine, like most antiarrhythmic agents, is basic and largely bound to alpha-1-acid glycoprotein (AAG); as noted elsewhere in the text, the concentration of AAG in plasma may vary widely. Under these circumstances free rather than total drug concentrations may be more closely related to pharmacologic effect.

Garfinkel et al.[21] found serum concentrations of quinidine of about 11 μg/ml with no evidence of adverse effects in a patient who had undergone cardiac surgery following an acute myocardial infarction. AAG levels at this time were elevated considerably and the free fraction of quinidine was only 0.03; values in healthy subjects range from 0.07 to 0.13. The patient showed no signs or symptoms of toxicity presumably because the concentration of free quinidine was in the therapeutic range.

Lidocaine. Lidocaine is the most frequently used intravenous antiarrhythmic agent for the short-term management of ventricular arrhythmias; it is usually the drug of choice following acute myocardial infarction. Lidocaine is also used prophylactically after myocardial infarction to prevent or reduce the likelihood of primary ventricular fibrillation or tachycardia.

The half-life of lidocaine is about 2 hr but may be considerably longer in patients with reduced cardiac output and/or hepatic blood flow rate. In some patients, the clearance of lidocaine decreases with continuous infusion; dosage reduction may be required during therapy. Coadministration of cimetidine or propranolol, which decreases liver blood flow and inhibits hepatic metabolism, may also require dosage reduction of lidocaine. The clinical pharmacokinetics of lidocaine has been reviewed by Benowitz and Meister.[22]

Plasma levels of lidocaine less than 1.5 μg/ml are usually ineffective. The usual therapeutic lidocaine concentration range is 1.5 to 4.0 μg/ml, but levels up to 8 μg/ml may be needed in refractory patients. These higher concentrations may be associated with central nervous system (CNS) toxicity and cardiovascular depression. Lidocaine levels exceeding 8 μg/ml may be associated with seizures and serious cardiovascular disturbances.

The usefulness of monitoring plasma lidocaine concentrations is controversial. There is general agreement that no need exists for monitoring when the lidocaine infusion is no longer than 12 hr in duration. Richens and Warrington note that:[10]

> Plasma concentrations of ligocaine (lidocaine) are of limited value in clinical practice. The drug is almost always given intravenously, so variability in absorption does not occur. It is given only to patients under close supervision, and is rarely continued for more than a few days. It is therefore much easier to monitor the pharmacologic effects of the drug than with long term oral antidysrhythmic therapy.

According to Benowitz and Meister,[22] measurements of plasma lidocaine concentrations may be

useful in the following situations: (1) in patients in shock who may have markedly reduced clearance; (2) during prolonged infusion (>24 hr), especially in patients with cardiac or hepatic failure; and (3) in assisting in the clinical diagnosis of lidocaine toxicity in the presence of ambiguous signs and symptoms.

One study examined serum lidocaine levels and lidocaine effects in 33 patients in a coronary care unit.[23] Deglin and co-workers concluded that it is difficult to adjust lidocaine dosage during therapy on the basis of clinical assessment of the patient and rhythm monitoring alone. On the 8 occasions in which the diagnosis of a lidocaine toxic reaction was clinically considered, serum levels were greater than 8 μg/ml in 4 but less than 5 μg/ml in 3. In another study, 38 of 69 blood samples that the house staff predicted would be within the therapeutic range were indeed between 1.2 and 5 μg/ml, but 10 were between 5 and 9 and 7 samples were above 9 μg/ml. Each of these 7 patients exhibited signs consistent with lidocaine toxicity; however, in every instance there were associated disease symptoms, including hypoxia, inadequate cerebral perfusion, CNS depression, tremor, and orthostatic hypotension, that masked the adverse drug reactions.[23]

Plasma protein binding of lidocaine varies considerably because, like quinidine, it is largely dependent on circulating levels of AAG. Although free concentration of lidocaine may be more useful than total concentration, available methods for determining binding are too time consuming to be of value.

As an alternative, Routledge et al. examined whether AAG measurements could be used to estimate lidocaine binding indirectly.[24] A free lidocaine index was developed on the basis of measurements of plasma lidocaine and AAG in plasma samples from patients admitted to coronary care and given lidocaine prophylactically. The free fraction of lidocaine in plasma was determined by equilibrium dialysis.

Levels of AAG in plasma ranged from 50 to 250 mg/dl. Free fraction (F) was related to AAG and total lidocaine levels (T) as follows:

$$1/F = 1.45 + 0.023\,(AAG) - 0.129\,(T)$$

This relationship was used to calculate the free lidocaine index, defined as $F \times T$. A highly significant relationship ($r = 0.93$) was found between predicted and observed values of free concentration of lidocaine.

Table 15–1. Recommended Lidocaine Infusion Rates According to Clinical Classification of Heart Failure*

Clinical class	Infusion rate (μg/kg per min)	
	Minimum	Maximum
I	35	88
II	12	35
III, IV	5	12

*From Zito, R.A., and Reid, P.R.: Lidocaine kinetics predicted by indocyanine green clearance. N. Engl. J. Med., 298:1160, 1978. (Reprinted by permission of The New England Journal of Medicine.)

Although there is controversy regarding the need for monitoring plasma lidocaine concentrations, there is general agreement that better guidelines are desirable for individualizing the initial infusion rate of lidocaine. Zito and Reid showed a close relationship ($r = 0.95$) between the clearances of the indocyanine green (ICG) and lidocaine.[25] Because ICG clearance can be determined rapidly and easily, a test dose of ICG might be given before lidocaine therapy to estimate the clearance and the required infusion rate of lidocaine. As these results could not be confirmed by Bax and co-workers,[26] however, the value of this method is uncertain.

With some drugs there is a strong correlation between clearance at steady state and the concentration in blood or plasma at a certain time after a bolus test dose.[27] The critical time for sampling after a single test dose depends on the half-life of the drug. This one-point method of predicting clearance and steady-state concentration of a drug appears to apply to lidocaine.[28] A close relationship was observed between the plasma lidocaine concentration at 1 hr after a loading dose of 225 mg over 20 min and 2 mg/min thereafter and the patient's lidocaine clearance after 12 hr of infusion. Using this relationship prospectively, it was possible to alter the infusion rate to achieve a mean plasma lidocaine concentration of 3.69 ± 0.14 (s.d.) μg/ml at 12 hr in 6 subjects, close to the desired concentration of 3.5 μg/ml.[29] This approach may reduce the incidence of inadequate or excessive plasma lidocaine concentrations.

Lidocaine infusion rates may also be individualized based on population data from patients with different degrees of heart failure (Table 15–1).[25] Lopez and co-workers compared plasma lidocaine levels in a control group and in an experimental group who received an adjusted lidocaine regimen

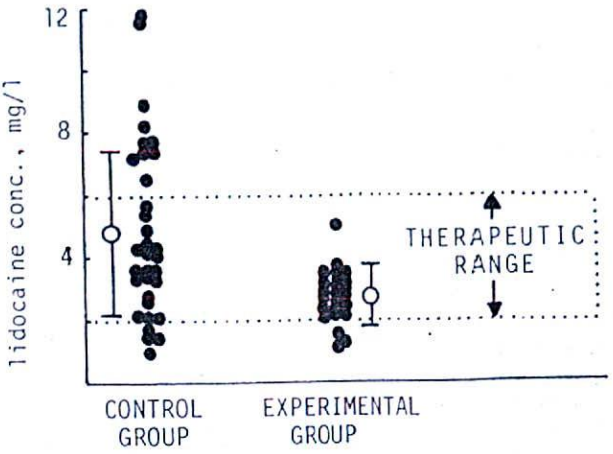

Fig. 15–2. Plasma lidocaine concentrations in a control group, dosed based on clinical judgment, and an experimental group who received an adjusted lidocaine dosage regimen based on the presence or absence of heart failure. Vertical bars denote the mean ± 1 standard deviation for each group. (Data from Lopez, L.M., et al.[30])

based on the presence or absence of heart failure.[30] Each group received a 1- to 2-mg/kg loading dose. Control patients were dosed using a conventional approach, receiving an infusion rate of 1 to 4 mg/min based on clinical judgment. Patients in the experimental group with no heart failure (Class I) received 35 to 88 μg/min per kg body weight; patients with Class II heart failure received 12 to 35 μg/min per kg body weight. The results are shown in Figure 15–2. This approach has merit, at least for some patients, and may be able to be extended to patients with Class III or IV heart failure.

Vozeh et al.[31] evaluated the performance of a computerized dosing approach to achieve a serum lidocaine concentration of 3.5 μg/ml, about the middle of the therapeutic range, in patients treated for acute ventricular arrhythmias. In all patients a blood sample to determine lidocaine levels was taken 2 hr after starting therapy. In about one-third of all patients, this information as well as population pharmacokinetic parameters served as input for a statistical program called Bayesian forecasting.[32] In the others, the physician considered the measured levels and altered the regimen as he or she deemed appropriate.

Both groups were similar with respect to average lidocaine concentrations 12 hr after starting therapy but interpatient variability was considerably larger in the control group. The 95% confidence intervals were 2.3 to 4.7 μg/ml in the computer-assisted group and 1.5 to 6.1 in the control group. Nine of the 41 patients in the control group had levels outside the recommended therapeutic range of 2 to 5 μg/ml, compared with only 1 of 22 patients in the Bayesian group. The investigators concluded that "Bayesian forecasting outperforms the physician in early adjustment of lidocaine dosage based on serum concentration measurements."

Flecainide. Flecainide is a class 1C orally effective antiarrhythmic agent. Therapeutic doses cause characteristic changes in the ECG. During the development of flecainide, correlations between trough plasma levels and suppression of ventricular ectopic beats were reported. Suggested minimal therapeutic levels of flecainide range from 200 to 400 ng/ml.

More recently, Salerno et al.[33] considered whether the side effects of flecainide correlated with drug plasma levels. They found that flecainide trough levels in plasma were higher when cardiovascular side effects were observed (mean 1063 ng/ml, range 296 to 2050 ng/ml) than when no adverse effects occurred (mean 609 ng/ml, range 89 to 1508 ng/ml).

The investigators defined the lower end of the therapeutic-toxic window as the flecainide level where there is at least 50% probability of efficacy and the upper end as the level where there is less than 10% probability of cardiovascular side effects. Under these conditions, they suggested a therapeutic range of 381 to 710 ng/ml.

The investigators concluded that "the risk of cardiovascular side effects increases at higher plasma levels of flecainide and is associated with greater increases in the PR and QRS intervals from baseline than are routinely observed during flecainide dosing . . . Fortunately, the close relationship of both therapeutic efficacy and cardiovascular side effects with level of flecainide and ECG intervals should make it possible to administer flecainide therapy with acceptable safety."

Another report, based on intravenous dosing regimens of flecainide concluded that plasma levels between 200 and 1000 ng/ml are associated with antiarrhythmic effects in most patients, but some require and tolerate higher levels and others manifest toxicity at "therapeutic" levels.[34]

Antibiotics

Evaluation of antibiotic therapy by monitoring plasma concentrations of drugs is controversial. According to Rylance and Moreland:[35]

> Blood levels of the antibacterial drugs may be presumed to be meaningful measures of drug effect only if bacteraemia is present. Otherwise, the blood concentration is only one of many determinants of drug effect. Other factors, which apply to other drugs too but to antibacterials in particular, are the blood flow to the infected site, the degree of drug protein binding, and penetration of the drug into abscesses, cells, and interstitial fluids.
>
> For optimal effect, drug levels should exceed the mean inhibitory concentration (MIC) for the likely or known causative organism by as great a margin as possible without undue risk of toxicity. However, it should be remembered that the MIC refers to a drug level in vitro, and although levels in excess of this are found in the blood, the levels in the infected tissue may be considerably lower. In addition, the controversy about whether high, but poorly sustained (peak), or lower, but adequate (continuous), levels should be achieved has not been resolved. Although a 'peak' regimen may aid in diffusion of drugs into poorly vascularised areas, and there is evidence that it is effective provided that the interval between doses is not unduly long, it remains unclear which method should be adopted and whether the mode of action of a drug (for example, bacterial wall synthesis inhibition or intracellular protein synthesis inhibition) should determine the type of regimen to be used.

Neu, in his review of practices in antimicrobial dosing, observed that erratic adherence to pharmacokinetic concepts has been the order of the day.[36] The only general guideline in effect today is that new antibiotics similar to established antibiotics but eliminated more slowly tend to be given less frequently. Interesting ideas regarding the use of pharmacokinetics in the development of dosage regimens for antibiotics in general,[37] and for cephalosporins in particular,[38] have been presented but await testing. Of the many antibiotics and other antibacterial drugs available, a case for monitoring plasma drug levels can only be made for the aminoglycoside antibiotics and, in some circumstances, chloramphenicol.[35]

Aminoglycoside Antibiotics. An extensive review of the clinical pharmacokinetics of aminoglycoside antibiotics has been presented by Pechere and Dugal.[39] Comprehensive commentaries on therapeutic drug concentration monitoring for aminoglycosides are also available.[40–44]

The aminoglycoside antibiotics are effective in treating pneumonia, urinary tract, soft tissue, burn wound, and other systemic infections caused by gram-negative organisms. In life-threatening infections, they are often combined with either β-lactam antibiotics or clindamycin. Gentamicin and tobramycin are among the most widely used antibiotics in hospitalized patients. Amikacin is used less frequently but is often useful against gentamicin- and tobramycin-resistant isolates. All aminoglycosides are ototoxic and nephrotoxic and have a relatively low therapeutic index.

The major elimination route for the aminoglycosides is renal excretion, largely by way of glomerular filtration. The half-lives of gentamicin, tobramycin, and amikacin in patients with normal renal function are variable but average about 2.5 hr. Patients with impaired renal function eliminate the aminoglycosides more slowly and require reduced dosage. Infants less than 7 days of age and elderly patients also require lower dosages.

Therapeutic aminoglycoside concentration monitoring appears to be useful for optimizing efficacy; whether it is also useful for reducing toxicity is controversial. It is generally held that appropriate treatment of serious systemic infections with gentamicin or tobramycin requires steady-state peak concentrations of 6 to 10 μg/ml and trough concentrations of 0.5 to 1.5 μg/ml. The corresponding values for amikacin are 20 to 30 μg/ml and 1 to 8 μg/ml, depending on the infection. It has been argued that monitoring of plasma aminoglycoside levels is needed because some patients, perhaps as many as 30 to 50% of all patients with normal renal function, require higher daily doses of gentamicin or tobramycin than the recommended 3 to 5 mg/kg per day to attain therapeutic concentrations.[40,43]

Moore et al.[45] examined the association of ami-

Table 15–2. Suggested Changes in Dose or Dosing Interval Based on Measured Serum Aminoglycoside Concentration*

Measured serum concentrations compared to desired values		Suggested change in dosing regimen	
Trough	Peak	Dose	Dosing Interval
Desired	Desired	No change	No change
Higher	Higher	Decrease or no change	Increase
Higher	Lower	Increase	Increase
Lower	Lower	Increase or no change	Decrease
Lower	Higher	Decrease	Decrease
Desired	Higher	Decrease	No change
Desired	Lower	Increase	No change
Higher	Desired	No change or increase	Increase
Lower	Desired	No change or decrease	Decrease

*From Cipolle, R.J., Zaske, D.E., and Crossley, K.[43]

noglycoside levels with mortality from gram-negative bacteremia. Each patient received a single aminoglycoside combined with a penicillin or cephalothin. Aminoglycoside levels in plasma were measured 24 to 48 hr after the start of treatment and were considered to be therapeutic when peak concentration of gentamicin or tobramycin exceeded 5 μg/ml and when the peak concentration of amikacin exceeded 20 μg/ml.

Twelve of the 89 patients died during antibiotic therapy or within 24 hr of its termination. Various factors were found to significantly influence mortality. Stepwise linear discriminant analysis of these factors indicated that the severity of the underlying illness was the strongest discriminator between death and survival. Next in importance was peak aminoglycoside concentration.

Plasma aminoglycoside levels were available for 84 patients, 10 of whom had died. Only 1 death occurred in 41 patients with early therapeutic levels of gentamicin, tobramycin, or amikacin, whereas 9 deaths were recorded in 43 patients with subtherapeutic concentrations; the corresponding mortalities were 2.4% and 20.8%. The results suggest that achieving adequate aminoglycoside levels, particularly within the first 48 hr of antibiotic therapy, in patients with gram-negative bacteremia may significantly improve the patient's chances of survival.

The relationship between plasma aminoglycoside concentration and toxicity is not clear. One school of thought proposes that among the risk factors for aminoglycoside toxicity are age, renal impairment, prior exposure to aminoglycosides, duration of treatment, total daily dose, cumulative dose, and elevated peak and trough plasma concentrations. The advocates of this school believe that aminoglycoside toxicity is reduced when peak concentrations of gentamicin or tobramycin are kept below 12 to 15 μg/ml and when trough concentrations do not exceed 2 μg/ml; the corresponding concentrations for amikacin are 30 μg/ml and 8 μg/ml. Cipolle et al.[43] recommend therapeutic aminoglycoside concentration monitoring during therapy and dosage adjustments, according to Table 15–2, when the peak or trough concentration deviates from the guideline. Some studies that support this idea include the work of Echeverria and co-workers who found that peak serum gentamicin concentrations greater than 12 μg/ml were significantly associated with ototoxicity in children,[46] and the work of Smith and associates who found that peak levels of amikacin greater than 38.5 μg/ml or of gentamicin greater than 10 μg/ml and trough levels of amikacin above 10 μg/ml were associated with nephrotoxicity.[47]

Other studies have failed to find a relationship between plasma aminoglycoside concentration and toxicity and support another school of thought that questions the value of therapeutic aminoglycoside concentration monitoring in reducing the risk of toxicity. An investigation of 201 critically ill patients during 267 courses of gentamicin or tobramycin reported that no clinical parameters, including plasma levels, were of value in predicting nephrotoxicity.[48] These investigators observed:

> Early concentration versus toxicity studies are difficult to interpret since oto- and nephrotoxicity were correlated with serum peak concentrations measured after serum creatinine was already rising. Since serum creatinine rise is a result of established nephrotoxicity, these studies did not establish serum concentration ranges which produce toxicity.

Schentag et al.[48] also noted that the controversy regarding the ability of peak aminoglycoside concentrations to predict nephrotoxicity also applies

to the value of trough concentrations to predict toxicity.

Advocates of this school believe that the nephrotoxicity of aminoglycosides is associated with an unusual ability of the kidneys to accumulate the drug that is characteristic of certain patients. If these patients could be identified, they could be treated with alternative antibiotics (e.g., third-generation cephalosporins). Careful examination of plasma level data suggests that, during therapy but before nephrotoxicity, trough levels of aminoglycosides rise more rapidly in these patients than in other patients. This hypothesis, however, requires further study.

Although plasma level monitoring of aminoglycosides is controversial, target plasma concentrations related to efficacy or to both efficacy and toxicity are often used to guide initial dosage recommendations. Nomograms based on an individual's creatinine clearance and lean body weight are available for gentamicin and tobramycin[49] and for amikacin.[50]

Some investigators carry out a pharmacokinetic study on an initial test dose of aminoglycoside to determine the clearance, half-life, and apparent volume of distribution of the drug in the patient. These parameters are then used to determine the required daily dosage and frequency of dosing for the individual.[43] Desired concentrations of gentamicin are attained in significantly more patients with this individualized pharmacokinetic method than with nomograms based on patient characteristics.[51]

Vancomycin. The increasing prevalence of infections caused by methicillin-resistant strains of *Staphylococcus aureus* has dramatically increased the use of vancomycin. Because of its potential to cause nephrotoxicity and ototoxicity, there has been considerable interest in developing appropriate dosing guidelines for vancomycin. Ototoxicity has been observed when peak serum levels of vancomycin are greater than 80 to 100 μg/ml; trough levels higher than 20 to 30 μg/ml have been associated with nephrotoxicity. Peak levels of 30 to 40 μg/ml and trough levels of 5 to 10 μg/ml are recommended.[52]

Several approaches have been developed to achieve optimal levels of vancomycin. These methods have been evaluated by Zokufa et al.[52] and Ackerman.[53] Zokufa and his colleagues found that most methods underpredicted vancomycin clearance. They concluded that a simple approach using a dose of 8 mg/kg (rounded to the nearest 50 mg) and a dosing interval based on creatinine clearance seemed to work best, and that this approach should be considered, at least for initial dosing of vancomycin. Even this method, however, is likely to produce trough and peak concentrations outside the therapeutic range in a large number of patients.

Both Ackerman and Zokufa et al. agree that early serum concentration monitoring and adjustment of initial algorithm- or nomogram-derived doses is necessary to assure safe and effective vancomycin serum concentrations. Whether or not routine monitoring of serum vancomycin concentrations is justified, however, is controversial.

Rodvold et al.[54] have concluded that routine monitoring of vancomycin concentrations is justified for most patients and that it is particularly important in critically ill patients. In their hospital, they monitor vancomycin levels once the patient has reached steady-state and once a week thereafter. More frequent monitoring occurs when the patient's status is changing. Edwards and Pancorbo,[55] on the other hand, have argued that the relationship between serum vancomycin levels and either efficacy or adverse events is not sufficiently compelling, given the costs, to recommend routine monitoring. They qualify their conclusion, however, by suggesting that in patients "demonstrating a poor therapeutic response, [and] those in whom unusually high MIC values have been documented, measurement of vancomycin concentrations may be justified."

Anticonvulsants

For most epileptic patients, long-term drug therapy is the only practical form of treatment. Therapy usually continues for at least 3 years and often for a lifetime. In many clinics and institutions, monitoring of plasma anticonvulsant levels is a part of the routine management of patients with epilepsy. It is generally held that monitoring has led to a more rational approach to drug therapy for convulsive disorders, resulting in better control of seizures, less drug toxicity, and use of fewer drugs. Dozens of reviews and commentaries on the clinical pharmacokinetics and therapeutic drug concentration monitoring of anticonvulsants are available.[50,57,58]

Carbamazepine. Originally developed for relief of pain associated with trigeminal neuralgia, carbamazepine was approved in 1974 for the treatment of convulsive disorders. It is used in both adults

and children for prophylaxis of grand mal and complex partial seizures. Carbamazepine is poorly water-soluble; oral doses are slowly but completely absorbed. It is extensively metabolized; less than 2% of a dose is found unchanged in the urine.

An epoxide with anticonvulsive activity is carbamazepine's principal plasma metabolite. Carbamazepine stimulates its own metabolism and, as a result, observed steady-state plasma concentrations are only about half of the concentrations predicted based on carbamazepine clearance after a single dose. Clinically, this is of little consequence because carbamazepine therapy is initiated with small doses that are gradually increased to a maintenance level over 3 to 4 weeks.

The half-life of carbamazepine at steady state is reported to be variable (5 to 27 hr); the recommended daily dose for adults varies 2-fold (7 to 15 mg/kg) and is usually given twice a day. Children metabolize the drug more rapidly than adults and may need to receive the drug 3 or 4 times a day. Adult patients taking other anticonvulsants (enzyme-inducing agents) may also need a higher daily dosage and more frequent administration.

Therapeutic drug concentration monitoring of carbamazepine has been reviewed by MacKichan and Kutt.[59] The therapeutic concentration range of carbamazepine is reported to be 4 to 12 μg/ml. It has been suggested that plasma concentrations of both carbamazepine and its epoxide metabolite might correlate better with therapeutic and toxic effects but knowledge of the activity of the metabolite is limited.

Theodore et al.[60] studied the relation of plasma levels of carbamazepine and carbamazepine epoxide as well as their ratio to drug toxicity and seizure control in patients with complex partial seizures. Patients receiving only carbamazepine showed a significant correlation between the levels of parent drug and its epoxide. In turn, the serum concentration of each, as well as their sum and ratio, was significantly correlated with toxicity scores and seizure frequency. The investigators concluded that measurement of epoxide levels did not provide additional information useful for monitoring clinical response to carbamazepine therapy.

When patients were taking other anticonvulsants, the ratio of epoxide to parent drug was higher than that seen in patients on monotherapy, largely due to lower levels of carbamazepine. The investigators recommended that rather than assume the decrease in carbamazepine levels resulting from coadministration of enzyme inducing agents would be compensated by increased levels of epoxide, it is more appropriate to increase the carbamazepine dose to maintain plasma levels in the therapeutic range. "The contribution of carbamazepine epoxide to the therapeutic effect of carbamazepine is uncertain, and the role of carbamazepine epoxide plasma levels has not been established."[60]

Generally, carbamazepine concentrations of 4 to 8 μg/ml are considered adequate in patients receiving other anticonvulsant drugs; concentrations of 8 to 12 μg/ml are recommended in patients on monotherapy with carbamazepine. Carbamazepine serum levels exceeding 12 μg/ml are associated with a high incidence of incapacitating neurologic side effects. Concentrations exceeding 8 μg/ml are associated with carbamazepine toxicity when other anticonvulsants are also prescribed.[61]

Plasma carbamazepine concentrations may be monitored indirectly by determining carbamazepine concentration in saliva and relating it to plasma concentration. There has been interest in therapeutic drug concentration monitoring in saliva because it offers a noninvasive alternative to venepuncture and because, under some circumstances, it provides a measure of free rather than total drug concentration in plasma.[62]

In most cases, the relationship between saliva concentration and free or total drug concentration in plasma has been found to be too variable to be of predictive value. Carbamazepine may be one of the few drugs that is suitable for therapeutic monitoring in saliva.[63] Saliva sampling is likely to be of clinical value when venepuncture is difficult or undesirable (e.g., in children). In 11 studies, the correlation coefficient between saliva and plasma concentrations ranged from 0.83 to 0.97, averaging 0.92. Carbamazepine concentration in saliva is about 30% that in plasma, consistent with the fact that the free fraction (fraction unbound to plasma proteins) in plasma is about 0.3. The therapeutic carbamazepine concentration range in saliva is suggested to be 1.2 to 3.5 μg/ml.[63]

Enthusiasm for monitoring free rather than total serum concentrations of carbamazepine was dampened by a report from Froscher et al.[64] These investigators studied more than 200 patients receiving carbamazepine monotherapy and considered the relationship of free and total drug levels with therapeutic outcome and side effects. They found no closer correlation between free concentration and seizure reduction or side effects than between

total concentration and effectiveness or side effects. Whether monitoring free drug is advantageous when more than one anticonvulsant is used has not been determined.

Ethosuximide. Ethosuximide is specifically indicated for the treatment of patients with absence (petit mal) seizures. It is extensively metabolized but no active metabolites have been reported. Highly variable half-lives of ethosuximide have been observed, ranging from 14 to 72 hr. The average half-life of ethosuximide is 30 hr in children and 50 to 60 hr in adults. Most patients can be dosed with ethosuximide once a day.

The use of plasma ethosuximide levels as a guide to drug therapy has been reviewed by Stoehr and Sherwin.[65] Plasma concentrations of 40 to 100 μg/ml have been associated with ethosuximide efficacy. No relationship has been established between toxicity and plasma levels of ethosuximide but most patients who fail to respond at concentrations of about 100 μg/ml do not benefit from higher concentrations. There have been conflicting reports on the value of saliva concentration monitoring of ethosuximide.[63]

Phenobarbital. In general, phenobarbital is effective in all convulsive disorders except petit mal seizures; it has been used as an anticonvulsant drug since 1912. About two thirds of a dose of phenobarbital is metabolized and the rest is excreted in the urine. The half-life of phenobarbital ranges from 50 to 120 hr in adults and from 40 to 70 hr in children. Because of its long half-life, phenobarbital is usually given to adults once a day at bedtime. Children sometimes require twice-a-day dosing. Approximately 2 to 3 weeks may be required to reach steady-state levels of phenobarbital in plasma.

Therapeutic drug concentration monitoring of phenobarbital has been reviewed by Saunders and Penry.[66] Plasma concentrations of 15 to 40 μg/ml are usually required for adequate therapeutic effect. Plasma phenobarbital levels exceeding 60 μg/ml result in lethargy, stupor, or coma, but habitual barbiturate abusers may tolerate much higher concentrations. In fact, the upper limit of the therapeutic concentration range of phenobarbital is not clearly defined because of the wide variation in tolerance to the sedative and hypnotic effects of the drug. Whether or not tolerance develops to the anticonvulsant effect of phenobarbital is not known. It is generally agreed that the value of monitoring phenobarbital levels is less than that for phenytoin.

Primidone. Uncertainty exists regarding the anticonvulsant effect of primidone as distinct from the effects of its principal metabolites. Primidone is extensively metabolized; both of its major metabolites, phenobarbital and phenylethylmalonamide, have anticonvulsant activity.

Levels of 5 to 12 μg/ml have been suggested as the therapeutic plasma concentration range for primidone.[66] These levels, however, are usually associated with plasma phenobarbital concentrations within the phenobarbital therapeutic concentration range (15 to 40 μg/ml). At this time, there seems to be no clear indication for measuring primidone concentration in plasma, but there may be some value in monitoring plasma phenobarbital levels during primidone therapy.

Phenytoin. No drug has a greater need for therapeutic drug concentration monitoring and individualized dosing than phenytoin. A relationship between drug concentration in plasma and daily dose is almost nonexistent because phenytoin is poorly absorbed, highly plasma protein bound, and subject to nonlinear, capacity-limited metabolism. Despite these problems, it is the most frequently prescribed anticonvulsant drug for the management of grand mal and partial seizures.

The value of therapeutic drug concentration monitoring for phenytoin has been reviewed by Winter and Tozer[67] and by Finn and Olanow.[68] Optimum phenytoin efficacy is achieved in most patients with serum concentrations in the range of 10 to 20 μg/ml. Only 20% of a typical patient population will have steady-state serum phenytoin concentrations in the therapeutic range if given the usual 300-mg daily dose.[67] An additional 30% will have levels between 5 and 10 μg/ml and may derive some benefit from the drug; however, this dose is clearly subtherapeutic for at least 27% of the patients and produces excessive serum concentrations that are likely to result in adverse effects in 16% of the patients. Daily phenytoin dosages as small as 125 mg or as large as 600 mg may be required to produce therapeutic concentrations in a given patient.

Tables 15–3 and 15–4 show the relationship between plasma phenytoin concentration and the degree of seizure control; Table 15–3 also shows the poor correlation between dose and efficacy of phenytoin.[69] Relatively small changes in plasma phen-

Table 15–3. Number of Epileptic Seizures During 2 Months in Relation to Mean Prescribed Dose and Plasma Concentration of Phenytoin*

No. of seizures	No. of patients	Prescribed dose (mg/kg per day)	Phenytoin concentration (μg/ml)
0	84	5.0	13.4
1	19	5.7	8.8
2	23	4.8	7.3
3–5	11	4.4	4.5
>5	11	6.4	6.2

*Data from Lund, L.[69]

ytoin levels can dramatically affect the frequency of seizures.

Concentration-related CNS toxicity of phenytoin is generally observed at serum concentrations above 20 μg/ml. As serum levels rise, so do the frequency and severity of side effects (Fig. 15–3).[70] Nystagmus is generally the earliest side effect detected, and is seen at levels of 15 to 30 μg/ml. Ataxia usually occurs at levels greater than 30 μg/ml; somnolence and diminished mental capacity are seen at levels exceeding 40 μg/ml.

The most common adverse effect of phenytoin therapy is gingival hyperplasia, which may lead to impaired mastication and malocclusion. This condition is said to occur in more than 40% of the patients taking the drug and may be more common in children. Gingival hyperplasia during phenytoin therapy appears to be a direct effect of phenytoin on gingival tissue. The relationship between serum phenytoin concentration and the severity of gingival hyperplasia is shown in Table 15–5.[71]

Despite the wide variation in serum levels of phenytoin in response to a given dose, there are few guidelines for initiating phenytoin dosage and most patients are started on 300 mg/day. Children metabolize phenytoin more rapidly than do adults and may require 2 or 3 times larger mg/kg daily doses (up to 15 mg/kg per day) than do adults. The dosage of phenytoin may need to be increased during pregnancy because of the increased clearance of the drug during this period.

Table 15–4. Relationship Between Degree of Seizure Control and Plasma Phenytoin Concentration Interval*

Phenytoin concentration (μg/ml)	No. of patients	No. of patients without seizures during 2 mo	Seizure-free (%)
0 to 9.9	95	41	43
10.0 to 19.9	33	24	72
above 20.0	20	19	95

*Data from Lund, L.[69]

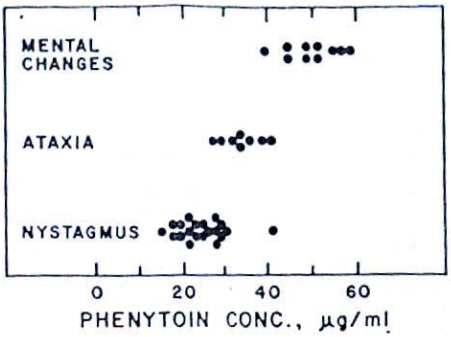

Fig. 15–3. Phenytoin levels in blood at the time patients experienced certain adverse effects of the drug. (Data from Kutt, H., et al.[70])

Because most patients are started on the same initial dosage of phenytoin and because this dosage regimen is likely to produce serum phenytoin levels that are outside the therapeutic concentration range in about three fourths of the patients, most patients benefit from a determination of phenytoin concentration in serum 2 weeks after initiating therapy. When the plasma levels are low and seizure control is inadequate or when plasma levels are high and there are signs of phenytoin toxicity, it is usually desirable to modify the dosage regimen.

Unlike the dosage adjustment for most drugs, that for phenytoin in response to plasma levels outside the therapeutic range and clinical signs is not a simple matter of ratio and proportions. Ordinarily, one might think that a patient showing less than optimal seizure control and a serum level of 8 μg/ml would require a doubling of the dosage to bring the levels up to a range of 15 to 20 μg/ml. This is not so for phenytoin because it is eliminated by capacity-limited metabolism. A doubling of the dosage under these conditions in most patients would produce excessive, potentially toxic serum phenytoin levels. Some patients may need as little as a 50-mg increment to the usual daily dose to

Table 15–5. Dose and Serum Levels of Phenytoin in Patients with Gingival Hyperplasia*

Grade of hyperplasia	No. of patients	Dose (mg/kg)/day	Phenytoin concentration (μg/ml)
0	75	3.0	3.0
I	26	3.4	3.8
II	99	4.4	9.5
III	27	5.7	18.4

*Data from Kapur, R.N., et al.[71]

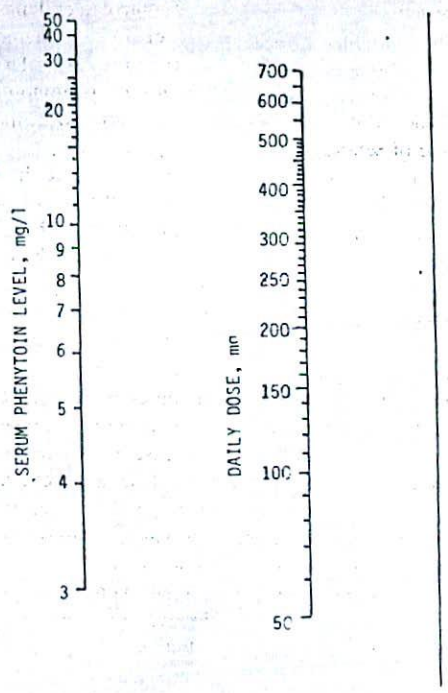

Fig. 15–4. Nomogram for predicting the daily dose of phenytoin required to achieve a desired serum level when a reliable serum level on a given daily dose is known. A line is drawn connecting the observed serum level (left-hand scale) with the administered dose (center scale) and extended to the right-hand vertical line. From this point of intersection, another line is drawn to the desired serum level (left-hand scale). The dose needed to produce this level is read off the center scale. (From Ramsteck, B., et al.: Predicting phenytoin dose. A revised nomogram. Ther. Drug Monit., *1*:325, 1979.)

bring the levels within the therapeutic concentration range. The same problem occurs when the dosage of phenytoin is reduced: in most patients, halving the dose will result in a greater than 50% decrease in serum phenytoin levels.

Many schemes have been proposed to estimate the change in phenytoin dosage required to bring the serum level to the therapeutic range once a reliable serum concentration on a given daily dose of phenytoin has been determined.[67,72–74] One nomogram is shown in Figure 15–4. Richens proposes that all patients be started on a small dose of phenytoin, 200 mg/day, and that the steady-state serum concentration of phenytoin be determined after 2 to 3 weeks.[76] If the drug level and clinical signs indicate a need for dosage change, this can be carried out by means of the nomogram in Figure 15–4.

All of the schemes proposed to adjust phenytoin dosage during therapy are imperfect.[72,73] Individual predictions may err on the high or low side; nevertheless, most seem to give better results than clinical judgment alone.

Of all the drugs for which therapeutic drug concentration monitoring has been advocated, phenytoin is the most compelling. Phenytoin is also one of a small number of drugs that is considered suitable for therapeutic monitoring in saliva. Many investigators have reported strong correlations between phenytoin concentrations in saliva and plasma.[63] In general, the average ratio of saliva to plasma concentrations is about 0.1, consistent with the fact that only about 10% of phenytoin concentration in plasma is not bound to plasma proteins. The therapeutic concentration range for phenytoin in saliva is 1 to 2 μg/ml. The main indications for using saliva phenytoin concentrations in therapeutic drug monitoring are in children and in patients with renal failure or hypoalbuminemia, where plasma protein binding is impaired so that total plasma concentration gives a false estimate of free drug concentration unless binding is determined.

The measurement of free rather than total phenytoin concentration is sometimes justified. Some hospitals have made available a routine monitoring service for determining free phenytoin levels in plasma. Peterson et al.[77] have examined the value of such services. Free phenytoin levels were determined when specifically requested by a physician, or when a determination of total phenytoin levels was requested but the patient's chart suggested the possibility of impaired plasma protein binding.

The percentage of free phenytoin in plasma in the study population ranged from 9 to 29%, with a median value of 14%. Total phenytoin concentration was in the therapeutic range (10 to 20 μg/ml) in only 30% of the patients, and below the range in more than half of the patients. On the other hand, because of the large number of patients demonstrating impaired binding of phenytoin, free levels were within the therapeutic range in about half of the cases and above the range in about 20% of the patients. The investigators concluded that the "use of the total phenytoin assay indicated that most patients needed increases in dosage, whereas the free phenytoin assay level showed that most

patients probably required no alteration in dosage or even a reduction."

The variability in plasma protein binding of phenytoin reported by Peterson and his colleagues is large; other investigators have found less variability, particularly in patients who are not hospitalized. For example, Rimmer et al.[78] observed that the percentage of free phenytoin in plasma in epileptic patients attending an outpatient clinic ranged from 12 to 18%.

These investigators concluded that "there appears to be very little variability in protein binding of phenytoin in epileptic patients and thus total plasma phenytoin concentration closely reflects the free (unbound) drug concentration. Routine estimation of free plasma phenytoin concentration is therefore unnecessary and should be reserved for those patients where alteration in binding is likely."

In another study, Theodore et al.[79] examined the relationship between total or free phenytoin levels and adverse effects in patients with seizure disorders. They also found relatively little variability in phenytoin binding to plasma protein. They reported a significant correlation ($r = 0.84$) between free and total phenytoin concentration. No relationship was found between the daily dose of phenytoin and drug toxicity, but significant partial correlations with adverse effects were seen for total ($r = 0.49$) and free ($r = 0.59$) phenytoin.

These investigators concluded that "free phenytoin measurements were only marginally better predictors of drug toxicity than were total plasma phenytoin levels. Therefore we suggest that neither clinical nor pharmacological considerations warrant routine monitoring of free phenytoin levels."

It is usually assumed that the type of epileptic seizure plays little or no role in defining the therapeutic concentration range for phenytoin or other anticonvulsants. Schmidt et al.[80] examined this assumption by monitoring plasma concentration of phenytoin in patients with various types of epileptic seizures. The mean plasma concentration needed for complete control of tonic-clonic seizures alone was 14 μg/ml, whereas a mean level of 23 μg/ml was necessary to control simple or complex partial seizures alone or together with tonic-clonic seizures. A similar trend was observed in patients treated with phenobarbital and with carbamazepine.

The investigators concluded that "higher plasma concentrations of phenytoin, phenobarbital, and carbamazepine are necessary for control in epilepsy with simple or complex partial seizures compared with epilepsy with tonic-clonic seizures alone. The efficacy of plasma concentrations of phenytoin, phenobarbital, and carbamazepine varies with the type of seizure."

Almost since the beginning of therapeutic drug monitoring, there has been concern that pharmacists or physicians would attempt to treat the blood level rather than the disease. For example, should the dose of an anticonvulsant be increased in patients with epilepsy who were free of seizures but had subtherapeutic serum levels? An attempt to answer this question was described by Woo et al.,[81] who randomized patients with tonic-clonic seizures treated with monotherapy (phenytoin or phenobarbital) and seizure-free for at least 3 mos to two groups, group one in which the dose and the level were maintained in the subtherapeutic range, and group two in which the dose was increased until the level was in the therapeutic range.

Over a period of 24 mos, there were no significant differences between the two study groups in the occurrence of seizures, but patients in group two had an increased incidence of neurotoxic side effects from the increased dose. The investigators concluded that "it is unnecessary to increase the dose of the antiepileptic drug despite a subtherapeutic serum concentration in relatively well-stabilized patients . . ."

Valproic Acid. This drug has a broad spectrum of antiepileptic activity; there is evidence that it acts by inhibiting enzymes involved in the degradation of gamma-aminobutyric acid (GABA) in the CNS.

Valproic acid is highly bound to plasma proteins, but binding is concentration-dependent; its volume of distribution may vary from 0.1 to 0.5 L/kg. Valproate is essentially eliminated by metabolism. The clearance (5 to 30 ml/hr per kg) and half-life (4 to 17 hr) of valproic acid are variable. Children appear to eliminate the drug more rapidly than adults. Phenytoin, phenobarbital, primidone, and carbamazepine significantly increase the clearance of valproic acid.

Optimal daily dosage of valproate may vary from 15 to 100 mg/kg; the dosing interval may vary from 6 to 24 hr. Children may require higher and more frequent dosage than adults. Patients on other anticonvulsant drugs may require larger doses than patients on valproic acid alone. Patients with severe hepatic disease require smaller than average doses.

The clinical pharmacokinetics of valproic acid has been reviewed by Gugler and von Unruh[82] and the use of plasma levels to guide valproate therapy by Cloyd and Leppik.[83] Data from several studies suggest that adequate seizure control requires serum valproate levels of at least 40 to 50 μg/ml.

The relationship between adverse effects and serum levels is not clear, but hepatotoxicity has been associated with serum valproic acid levels above 100 μg/ml. The most common side effects of valproate therapy, nausea, vomiting, and drowsiness, do not seem to be related to serum valproate levels. The therapeutic concentration range of valproic acid is considered to be 50 to 100 μg/ml.

Because the binding of valproic acid is variable, many investigators believe it would be more useful to monitor free rather than total drug concentrations in plasma.[84] Unfortunately, the correlation between saliva and total or free plasma valproate levels is poor. Other methods to determine free drug concentration in plasma are available but poorly validated and in limited use.

The development of ultrafiltration techniques has facilitated the determination of free drug concentration in serum. These advances prompted Froscher et al.[64] to reevaluate the clinical significance of free level monitoring of valproic acid. In keeping with the results of other studies, they found a close correlation between free and total levels of valproate and therefore no better correlation between free valproic acid and clinical endpoints than between total drug levels and the same endpoints.

Anti-Inflammatory Drugs

A large number of nonsteroidal anti-inflammatory and analgesic drugs are now available. All are indicated for the treatment of acute and chronic rheumatoid arthritis and osteoarthritis. Naproxen, tolmetin, and salicylate are also indicated for juvenile arthritis. The newer drugs seem to be similar in mechanism of pharmacologic effect to salicylate but most are considered more potent or less toxic than aspirin. Knowledge of pharmacokinetic characteristics has played a small role in therapy with these drugs because therapeutic outcome is difficult to assess and no clear concentration-response relationship has been defined. The half-life of these drugs is believed to be related to duration of effect; naproxen, which has a longer half-life than ibuprofen (13 hr vs 2 hr), is given twice a day rather than 3 or 4 times a day; piroxicam, with a still longer half-life is given once a day. Only in the case of salicylate has there been interest in monitoring serum drug concentrations during therapy; this interest is largely directed at avoiding side effects.

Salicylate. Salicylate is the active anti-inflammatory component of many drugs including aspirin, choline salicylate, choline and magnesium salicylates, magnesium salicylate, salsalate (salicylsalicylic acid), and sodium salicylate. Pharmacologically significant plasma levels of salicylate are also found in patients taking antidiarrheal mixtures containing bismuth subsalicylate.

At low therapeutic salicylate concentrations in plasma (10 mg/dl) about 90% is bound, whereas at high concentrations (40 mg/dl) only about 75% is bound to plasma proteins. Accordingly, the apparent volume of distribution of salicylate is concentration-dependent.

Only about 10% of a small dose of salicylate (300 mg or less) is excreted unchanged in the urine, but the fraction excreted is greater when higher doses are given because the metabolism of salicylate is capacity-limited. Accordingly, the apparent half-life of salicylate increases with dose and plasma concentration.

The renal excretion of high levels of salicylate is dependent on urine pH. Larger doses are needed for a patient with alkaline urine than for a patient with acid urine to achieve the same plasma levels of salicylate.

The monitoring of plasma concentrations of salicylate has been recently reviewed.[85,86] It can be seen in Figure 15–5 that plasma salicylate concentrations correlate with clinical and adverse effects of the drug; there is considerable overlap, however, between the effective concentration region and the region of concentration associated with adverse effects and toxicity. Assessment of a therapeutic concentration range for salicylate is complicated by concentration-dependent changes in plasma binding, changes in albumin levels, and concomitant drug therapy.

Some physicians determine maximum tolerated salicylate doses by gradually increasing the amount given until tinnitus is observed, then decreasing the daily dosage by 600 mg. In one study, 67 patients with rheumatoid arthritis were given gradually increasing doses of buffered aspirin until tinnitus was noted.[87] In 52 patients experiencing tinnitus, the average serum salicylate was 29.5 mg/dl (range 19.6 to 45.8). The majority of patients noted tinnitus when taking a daily dose of 4.5 to 7.2 g of

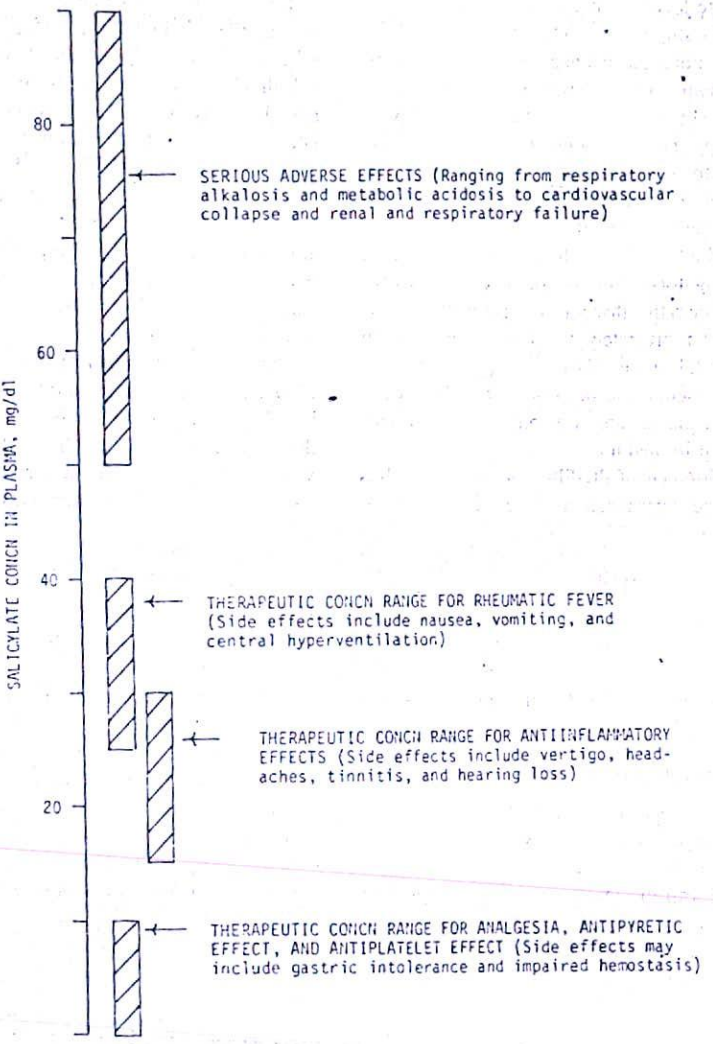

Fig. 15–5. Relationships between plasma salicylate concentrations, effects, and complications. (Data from Dromgoole, S.H., and Furst, D.E.[87])

aspirin (15 to 24 tablets per day), but some patients experienced tinnitus at doses as low as 3.6 g/day and as high as 10.8 g/day. Despite high daily doses, 15 patients did not note tinnitus. The average serum salicylate concentration in this group was 43.8 mg/dl (range 31 to 67.7). All 15 patients had pre-existing impaired hearing.

Reversible bilateral hearing loss is known to occur at serum salicylate levels exceeding 30 mg/dl. Patients with normal hearing, however, apparently experience tinnitus before any significant salicylate-induced hearing loss occurs. On the other hand, patients with pre-existing hearing loss apparently cannot hear the high-tone tinnitus characteristic of salicylate ototoxicity. These patients are at risk if salicylate therapy is guided by the clinical adage, "Push to tinnitus, then back off slightly."

It has been recommended that if there is any suggestion on history or physical examination of a hearing loss, serum salicylate levels rather than tinnitus should be used to guide salicylate dosage.[87] Moreover, any patient over the age of 50 yr who does not note tinnitus on a daily dose of 6 g of aspirin should have his serum salicylate level determined.

Although aspirin and other salicylate-containing compounds continue to be useful drugs, the dwindling incidence of rheumatic fever and the increasing use of alternative nonsteroidal anti-inflammatory drugs in the treatment of arthritic disease has resulted in far fewer indications for using high doses of salicylate and for measurement of plasma salicylate concentrations.

Indomethacin. In addition to its use in rheumatoid arthritis, indomethacin is also approved as an alternative to surgery in newborns with patent ductus arteriosus (PDA). Reasoning that inadequate blood levels of indomethacin may play a role in infants failing to respond to the drug, Brash et al.[88] studied the pharmacokinetics of iv indomethacin in 35 premature infants with symptomatic PDA.

Most infants responded to indomethacin with ductus constriction. Lack of efficacy in 6 patients was associated with a significantly higher clearance of indomethacin and a shorter half-life. Indomethacin levels in plasma less than 250 ng/ml at 24 hr after an iv dose were observed in 6 of 7 unsuccessful infusions. In contrast, 32 of 38 successful infusions resulted in indomethacin levels above 250 ng/ml at 24 hr.

Some reports have suggested that the ductus in older infants is less likely to respond to indomethacin. This does not appear to be a case of true resistance. The clearance of indomethacin increases with age and rapid clearance is a critical factor in treatment failure.

Cardiac Glycosides

Cardiac glycoside preparations officially recognized in the United States include powdered digitalis, digitoxin, digoxin, and deslanoside. They are indicated in the treatment of CHF and in the management of certain arrhythmias. Deslanoside is approved only for intravenous administration. Both intravenous and oral forms of digoxin are available. Digoxin is the most widely used form of digitalis.

All the cardiac glycosides are potent and have narrow therapeutic indices. Toxic manifestations include gastrointestinal and CNS symptoms and disturbances of cardiac rhythm. The use of individualized dosage and therapeutic drug concentration monitoring has been considered for digoxin and digitoxin.

Digoxin. One survey has shown that 22% of all medical patients receive digoxin; about 18% of these patients experience one or more side effects.[89] Another study indicates a 23% incidence of digoxin toxicity in treated patients.[90] The mortality rate in toxic patients is 40%, whereas the mortality rate in nontoxic patients is only 17%. The use of digoxin has decreased in recent years because of changes in treatment and availability of other drugs, but it remains a widely used drug. The incidence of digitalis toxicity has also decreased during the past decade because of a better understanding of the pharmacokinetic and pharmacologic characteristics of digoxin.

Oral digoxin is incompletely absorbed; absorption may be erratic in certain patients and with certain dosage forms. Bioavailability is considered to be a factor contributing to interpatient variability in clinical response. Digoxin is poorly bound to plasma proteins, only to the extent of about 25%, and has a large apparent volume of distribution (500 to 600 L). The volume of distribution of digoxin is 30 to 50% smaller in patients with renal failure. Digoxin distributes slowly; 8 to 12 hr may be required to reach equilibration between blood and tissues. In patients with normal renal function, the half-life of digoxin varies from 32 to 48 hr. About 50 to 70% of an intravenous dose is excreted

unchanged in the urine; the balance is subject to metabolism and biliary excretion.

Rapid digitalization calls for a loading dose, usually 1.0 to 1.5 mg divided into 2 or more doses given every 6 to 8 hr, followed by daily maintenance doses, usually 0.125 to 0.5 mg once a day. Smaller loading doses may be appropriate in patients with severe renal failure because of a reduced apparent volume of distribution. Dosage calculations for digoxin and other digitalis glycosides should be based on ideal rather than total body weight because these drugs are not taken up by adipose tissue. Larger loading and maintenance doses per kg body weight are used in infants and children up to 10 years of age. Maintenance dosage should be reduced in patients with impaired renal function and may require reduction in the elderly. Digoxin should be administered cautiously to certain patients who seem more sensitive to the effects of the drug (e.g., patients with low serum potassium).

More than 50 studies on the relationship between serum digoxin concentration and digoxin toxicity have been reported.[91] Based on these investigations the therapeutic serum digoxin concentration range is considered to be 0.5 to 2.5 ng/ml. Maintenance of serum digoxin levels between 1.0 and 1.5 ng/ml during therapy is considered ideal by some investigators. Digoxin toxicity is likely if serum levels are greater than 3 ng/ml and unlikely if the levels are less than 1 ng/ml. Similar guidelines apply to infants and young children, but infants tolerate higher serum digoxin concentrations than adults do without developing signs of digitalis toxicity.[92]

One of the earliest studies examining the relationship between digoxin toxicity and serum levels found that patients with cardiac rhythm disturbances from digoxin intoxication tended to be older and to have diminished renal function compared to a nontoxic group.[93] Despite comparable mean daily digoxin doses, intoxicated patients had a mean serum digoxin concentration of 3.7 ng/ml, whereas nontoxic patients had a mean level of 1.4 ng/ml. Of the patients with no evidence of toxicity, 90% had serum digoxin concentrations of 2.0 ng/ml or less; 87% of the toxic group had levels above 2.0 ng/ml.

In another study, serum digoxin concentrations were determined in 143 patients who were divided into 4 groups on the basis of clinical considerations, as follows: I, not toxic but in CHF (subtherapeutic); II, not toxic and not in CHF (therapeutic); III, possibly toxic; IV, definitely toxic.[94] Significant differences between the means were found among the different groups for the following variables: digoxin level, dose per kg body weight, and creatinine clearance. These data are shown in Table 15–6. Of all the independent variables, digoxin level was the best predictor of both subtherapeutic and toxic patients.

The two studies cited above and, in fact, the majority of studies have demonstrated that there is a significant difference between the mean values of serum digoxin concentration in patients with and without digitalis toxicity, but also that there is a variable overlap between the two groups. Toxicity has been observed in some patients with serum digoxin levels less than 1.5 ng/ml; other patients have tolerated levels exceeding 3 ng/ml with no manifestations of digitalis toxicity. Toxicity at low serum levels of digoxin has frequently but not always been associated with hypokalemia or myxedema. The absence of toxicity with apparently high serum levels of digoxin has sometimes been the result of determining digoxin concentration during the distributive rather than the postdistributive phase of the drug concentration versus time curve; blood for serum digoxin level determinations

Table 15–6. Laboratory Data for Patients Receiving Digoxin*†

Variable	Patient group			
	Subtherapeutic	Therapeutic	Possibly toxic	Definitely toxic
Weight (kg)	72.7	65.3	64.0	60.7
Creatinine clearance (ml/min)	62.4	60.9	47.2	41.5
Dose (mg/day)	0.234	0.260	0.292	0.316
Digoxin level (ng/ml)	0.95	1.49	2.53	3.32
Dose (ng/kg)	0.003	0.004	0.005	0.005

*Any two mean values not underscored by the same line are significantly different at the 95% level.
†Data from Huffman, D.H., et al.[94]

should be drawn at steady state, 12 to 24 hr after the daily dose.

Several commentaries have stressed the pitfalls in the interpretation of serum digoxin concentrations.[95-97] Another commentary, presenting a more balanced view, concludes that although not every patient receiving digoxin requires the measurement of a blood level, the serum digoxin level is a useful clinical tool when used with good judgment.[98]

Interest exists in using patient and population parameters to individualize the initial dosage regimen of digoxin, but these efforts have met with only limited success. Several studies have suggested that little of the variability in serum digoxin concentrations can be accounted for by dose, age, body weight, or renal function.[99-101] Nevertheless, these considerations may augment clinical judgment in patients with renal failure and in elderly patients.

Nicholson and co-workers have described a simple method for prescribing digoxin based on clinical information and patient characteristics.[102] Using this method, they found that about 72% of all patients are expected to achieve mean steady-state serum digoxin concentrations within the therapeutic range, 7% above the range, and 21% below. A sophisticated computer method for forecasting the dosage required to obtain desired serum digoxin levels based on patient characteristics and early determinations of serum digoxin concentrations has also been described.[103]

Snidero et al.[104] have documented the overuse of digoxin serum assays for ambulatory patients in Italy. These results probably reflect the general overuse of digoxin therapeutic drug monitoring in most western countries. Hallworth and Brodie[105] have clearly stated that "routine serum digoxin measurement is not necessary if the patient is clinically stable and renal function is unaltered."

These investigators examined nearly 1600 requests for digoxin measurement in 886 patients over a 1-year period in a general hospital in Glasgow. In a subset of 334 patients who had more than one blood sample assayed for digoxin, 51.5% were within the therapeutic range at the first measure compared with 56.3% at the last measure. These results cast doubt on whether measurements had influenced patient management.

Digitoxin. Digitoxin is far less prescribed in the United States than digoxin, but it is an important drug in other parts of the world. It has a much longer half-life than digoxin (120 to 216 hr) and is largely metabolized. Digitoxin may be a more useful drug than digoxin in patients with impaired renal function because dosage adjustments are unnecessary. Like digoxin, digitoxin is usually given as a divided loading dose, followed by daily maintenance doses.

The therapeutic serum digitoxin concentration range is considered to be 15 to 25 ng/ml; concentrations exceeding 35 to 40 ng/ml are frequently associated with adverse effects.[106] As with digoxin, there is considerable variation and overlap in serum digitoxin concentrations associated with toxicity and therapeutic response.

Cyclosporine

Cyclosporine is a selective immunosuppressant that has revolutionized organ transplantation. Comprehensive reviews of this agent are available.[107,108] Several excellent commentaries specifically concerned with therapeutic drug monitoring have also been published.[109-112] Yee and Kennedy[107] have presented an algorithm for dosing cyclosporine based on measurements of trough concentrations at steady state. These guidelines are helpful in some patients but there is no general consensus as to how to apply cyclosporine concentration data to patient care. Some success has been reported in linking cyclosporine serum levels to the prevention of graft-versus-host disease, a major cause of morbidity and mortality after bone marrow transplantation.[113]

Methotrexate

The clearance of methotrexate varies widely in children; a 7-fold difference has been reported in one study.[114] In another study, investigators found a 50 to 100% greater probability of clinical relapse in children with acute lymphocytic leukemia (ALL) in remission who rapidly cleared methotrexate, compared with those patients who eliminated methotrexate more slowly.[115]

More recently, Evans et al.[116] reported the results of their efforts to determine whether an optimal range of serum concentrations of methotrexate could be identified for patients with ALL receiving high-dose methotrexate therapy. The mean systemic clearance of methotrexate was 78 ml/min but varied considerably. Median steady-state levels in individual patients ranged from about 9 to 24 μM.

During a follow-up period that averaged 3.5 years from diagnosis, there were 34 relapses among the 108 patients, about two-thirds of which were hematologic relapses. Probability analysis revealed

that patients with median steady-state serum levels below 16 μM were about 3 times more likely to have a relapse of any kind during therapy and 7 times more likely to have a hematologic relapse than those with concentrations above 16 μM. Patients with low methotrexate concentrations were also more likely to have an early relapse.

The investigators concluded that "the results of this study indicate that the relative exposure to methotrexate . . . can have a significant influence on the probability of relapse in children with acute lymphocytic leukemia." They also noted that "although this study has not established a 'therapeutic' serum concentration or dosage of methotrexate in standard-risk ALL, we have identified a concentration that is more frequently associated with therapeutic failure (i.e., a 'subtherapeutic' range)."

Metoclopramide

Metoclopramide is a dopamine antagonist that stimulates upper gastrointestinal motility and enhances gastric emptying. Metoclopramide also has antiemetic activity and is used to treat nausea and vomiting associated with cancer chemotherapy, particularly with cisplatin.

To better understand and improve the effectiveness of metoclopramide for cisplatin-induced emesis, Meyer et al.[117] studied the relationship between serum metoclopramide levels and control of nausea and vomiting in patients with cancer. All patients received metoclopramide, 2 mg/kg intravenously every 2 hours for a total of 4 doses starting one-half hr before cisplatin was given.

Although the dose of metoclopramide was adjusted for body weight, serum levels varied a great deal, ranging from 200 to 2000 ng/ml. A clear relationship between metoclopramide concentration and antiemetic response emerged. Serum levels greater than 850 ng/ml immediately before the third dose of metoclopramide were associated with control of emesis in 78% of the patients and partial control in 18%. Control of emesis was not observed in any patient with serum levels of metoclopramide less than 850 ng/ml, but partial control was established in 42% of these patients. Increasing the dose of metoclopramide for nonresponders produced higher metoclopramide levels and improved clinical response in 4 of 5 patients. The investigators recommended that "if an assay for serum metoclopramide is available, we suggest that a level greater than 850 ng/ml will be needed just before the third dose for most patients."

Oral Anticoagulants

The oral anticoagulants include the coumarin derivatives, dicoumarol, phenprocoumon, and warfarin, and the indanedione derivatives, anisindione and phenindione. In the United States, warfarin is used almost exclusively. Phenprocoumon is a drug of choice in the United Kingdom and other parts of the world. The dosage of these drugs is always individualized according to prothrombin-time determinations. The usual therapeutic goal is to prolong prothrombin time by 1.5 to 2.5 times the control value or to reduce prothrombin activity to 15 to 35% of normal.

A higher incidence of bleeding in patients treated with warfarin in the U.S. than those treated in the UK prompted a major reexamination of anticoagulant targets. According to Hirsch,[118] "on the basis of current evidence, it would be reasonable to aim for a therapeutic range of 1.3 to 1.4 times control (equivalent to a prothrombin time of 14 to 17 seconds) with the rabbit-brain thromboplastin in common use in North America . . . " He also noted that "patients with venous thrombosis can be treated effectively and more safely by using a therapeutic range . . . of 1.3 to 1.4 times the control value rather than the formerly recommended range of 2.0 to 2.5 times control."

There are large interindividual differences in the clinical response to oral anticoagulants. The usual adult dose of warfarin varies from 2 to 10 mg a day; that of phenprocoumon from 0.75 to 6 mg a day. These differences are the result of variation in receptor affinity, in the availability of vitamin K and vitamin K-dependent clotting factors, and in the pharmacokinetics of the drug.[119–121]

Because of the long half-life of warfarin, treatment is usually started with a loading dose, typically 10 to 15 mg a day for 2 to 4 days. Thereafter, the daily maintenance dose is adjusted on a trial-and-error basis until the desired effect on blood coagulation has been achieved. Dosage titration is time consuming; until the optimum dosage is found, the patient is at risk either from the condition for which the anticoagulant is prescribed or from hemorrhage.

Routledge and co-workers investigated the possibility that a patient's response to a loading dose of warfarin might be used to predict his required daily maintenance dose.[122] They observed a strong correlation ($r = 0.90$) between the maintenance dose needed to achieve a thrombotest of 8 to 12%

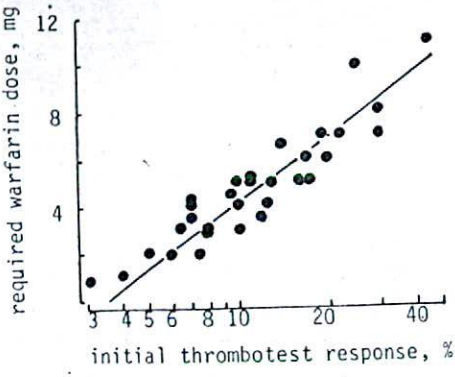

Fig. 15–6. Relationship between thrombotest response to an initial loading dose of warfarin (10 mg/day for 3 days) and the daily maintenance warfarin dose required to achieve anticoagulation at a thrombotest of 8 to 12%. (Data from Routledge, P.A., et al.[122])

and the log of the patient's thrombotest values 64 to 66 hr after the start of the warfarin loading regimen (Fig. 15–6). The theoretical basis for this relationship has been considered by Sawyer.[123] The relationship seems strong enough to have practical value in predicting warfarin dosage requirements in individual patients.

Psychotropic Drugs

Drugs used in the treatment of psychiatric disorders are often collectively called psychoactive or psychotropic agents. Antipsychotic or neuroleptic agents, like the phenothiazines, thioxanthenes, or butyrophenones, are used to treat psychoses, the most severe psychiatric illnesses; they have beneficial effects on mood and thought, but also carry the risk of neurotoxic effects that mimic neurologic diseases. Mood-stabilizing drugs (lithium salts) and mood elevating drugs (antidepressants) are used to treat affective disorders. Antianxiety-sedative agents, particularly the benzodiazepines, are used to treat anxiety states.

Although individualized dosage for the benzodiazepines is not common this is not the case for other psychotropic drugs. Among the antipsychotic agents, chlorpromazine dosage varies from 20 to 1000 mg a day and haloperidol dosage varies from 1 to 100 mg a day. The usual adult dose of amitriptyline is 50 to 300 mg a day. Dosage adjustments of these drugs are made on the basis of psychiatric response and adverse effects; pharmacokinetic factors or serum drug concentration measurements are rarely considered.[124] The adjustment of lithium dosage is an exception.

Many investigators have examined the relationship between serum levels of tricyclic antidepressants and clinical response. Whether serum drug concentration monitoring during tricyclic antidepressant therapy is worthwhile for some patients remains controversial. The application of pharmacokinetic principles to this large and diverse class of drugs has been limited by serum concentrations so low they are difficult to measure, active metabolites, indefinite clinical endpoints, and an incomplete understanding of pharmacologic mechanisms.

Antipsychotic Drugs. Dahl[125] and Sramek et al.[126] have presented reviews concerning the clinical utility of plasma level monitoring of antipsychotic drugs. Dahl noted that there have been some reports suggesting a relationship between therapeutic response and antipsychotic drug 'concentration' determined by means of a chemically nonspecific radioreceptor assay (RRA) that measures dopamine receptor-blocking activity in plasma. He pointed out, however, that most studies "have failed to demonstrate such a relationship, and the RRA does not seem to provide the generally useful tool for plasma concentration monitoring of antipsychotic drugs that was hoped for initially."

Other studies, using chemically specific assay methods, have, in most cases, also failed to demonstrate useful correlations. Among other problems, this approach does not consider the contribution of active metabolites to pharmacologic effect, which appears to be prevalent following the administration of most antipsychotic drugs.

According to Dahl, "reasonably controlled studies of plasma concentration-response relationships using randomly allocated, fixed dosages of chlorpromazine, fluphenazine, haloperidol, perphenazine, sulpiride, thioridazone, and thiothixene have been published but often involve relatively few patients . . . Plasma level monitoring of thioridazine and its metabolites . . . appears to have no clinical value . . .

"Non-responders and good responders to chlorpromazine treatment . . . have plasma drug concentrations in the same range . . . Therapeutic plasma haloperidol concentrations . . . in the range of 5 to 20 μg/L have been reported by some investigators, but others have found no such relationship . . . Unfortunately, there is no evidence that plasma concentration monitoring of antipsy-

chotic drugs may significantly reduce the incidence of tardive dyskinesia."[125]

Sramek et al.[126] pointed out that "the most impressive evidence to date for the presence of a neuroleptic therapeutic window is for haloperidol." This may relate to the relatively simple metabolic pathway of this drug compared with other antipsychotic agents. Volavka and Cooper[127] cautioned that "a therapeutic window for haloperidol may exist, but the evidence for it is inconsistent."

Virtually all studies agree that a haloperidol level of at least 5 ng/ml is required for efficacy in responsive patients. Some studies, however, suggest a need for levels of at least 20 ng/ml. One study suggested that benefit would derive with haloperidol levels as high as 50 ng/ml, whereas others report no benefit at levels above 15 ng/ml.[127] Perry et al.[128] recently reported that a serum haloperidol concentration in the range of 9 to 15 ng/ml was associated with a clinically important decrease in the rating scale used to evaluate the severity of schizophrenia. "Serum concentrations above this limit do not appear to either decrease or increase the probability of response."

Lithium. Lithium, in the form of lithium carbonate or lithium citrate, is an important drug for the treatment of mania and for the prevention of recurrent attacks of manic-depressive illness. Almost all of an oral dose of lithium is eliminated in the urine. The half-life of lithium is variable, averaging about 24 hr in patients with normal renal function. Because lithium distributes slowly from the blood and because lithium toxicity can occur with doses at or near therapeutic levels the daily dosage must be subdivided. Lithium carbonate capsules or tablets are usually given 3 times a day; an extended-release tablet is available for twice-a-day dosage.

The daily dosage of lithium varies widely depending on the severity of the disorder, the patient's response, and the ability to excrete lithium; a range of 150 to 3500 mg of lithium carbonate a day has been reported.[129] A more typical dosage range for responsive patients with normal renal function is 900- to 1800-mg lithium carbonate a day.

Determination of serum lithium concentration is a routine part of lithium therapy; it may be performed as often as twice a week during the acute phase of treatment until the clinical condition of the patient is stabilized. Effective serum levels during the acute manic phase are considered to be 1.0 to 1.5 meq per L; recommended maintenance serum lithium concentrations are 0.6 to 1.5 meq per L. Side effects may occur at serum lithium levels below 1.5 meq per L; mild to moderate toxicity may occur at levels from 1.5 to 2.5 meq. Serum lithium concentrations above 3 meq per L are associated with serious CNS disturbances and renal toxicity.[129,130]

Table 15–7. Dosages Required to Achieve a Steady-State Serum Lithium Level of 0.6 to 1.2 meq/L Based on the Serum Level of Lithium 24 hr after a Single Loading Dose of 600 mg Lithium Carbonate*

Initial serum level	Dosage required (mg)
<0.05	1200, three times a day
0.05 to 0.09	900, three times a day
0.10 to 0.14	600, three times a day
0.15 to 0.19	300, four times a day
0.20 to 0.23	300, three times a day
0.24 to 0.30	300, twice a day
>0.30	300, twice a day (with caution)

*Data from Cooper, Bergner, and Simpson.[131]

A predictive technique has been described that enables the estimation of a patient's lithium dosage requirement on the basis of a single blood sample collected 24 hr after the administration of a 600 mg initial dose of lithium carbonate.[131,132] The lithium dosage required to achieve a steady-state serum level of 0.6 to 1.2 meq per L based on the 24-hr serum lithium concentration after a single loading dose is shown in Table 15–7.

Recent review articles[133,134] suggest that the thinking on serum lithium monitoring has not changed in any important way. Schou,[133] in 1988, again concluded that "serum lithium monitoring is important for dosage adjustment during the start of treatment and for control after dosage changes." Lobeck,[134] who critically reviewed several methods to optimize the dose of lithium, concluded that "because of the number of factors influencing lithium disposition and the potential of these factors to change, even the best of methods would not eliminate the need routinely to monitor serum lithium concentration and clinical condition. Considering the shortcomings of the currently available methods, careful monitoring is imperative."

Cyclic Antidepressants. Several classes of drugs are useful in the pharmacologic treatment of depression. The tricyclics, including amitriptyline, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine, are the most widely used antidepressants. Maprotiline is a

closely related drug but chemically has a tetracyclic ring structure. Imipramine is also used in the treatment of childhood enuresis.

The tricyclics undergo considerable presystemic hepatic metabolism after oral administration; doxepin is subject to the greatest first-pass effect and protriptyline to the least. Presystemic metabolism contributes to the large intersubject variability in blood levels of tricyclics. All of these drugs are considerably bound to plasma proteins (> 90%) but have large volumes of distribution (10 to 30 L/kg) and low blood levels. The tricyclics are eliminated essentially by hepatic metabolism. Half-lives are relatively long; doxepin and imipramine have the shortest half-lives (10 to 25 hr) and protriptyline has the longest half-life (50 to 100 hr). All of these compounds produce active metabolites. Desipramine and nortriptyline are the demethylated metabolites of imipramine and amitriptyline, respectively. 2-Hydroxy imipramine, 2-hydroxy desipramine, and 10-hydroxy nortriptyline also have antidepressant activities.

Because of the long half-lives of these drugs, they may be given once a day, preferably at bedtime. Dosage of tricyclics must be individualized on the basis of clinical response and side effects; determination of serum tricyclic levels may or may not be useful in this process. Dosage probably should be reduced in the elderly because of a decrease in clearance. Patients on barbiturates and those who smoke may require a higher daily dosage.

The use of serum levels as a guide to treatment has been the subject of many review articles and commentaries.[135-140] These papers summarize and report a conflicting picture of the value of therapeutic drug concentration monitoring of tricyclic antidepressants. For example, reports on a relationship between serum concentration and clinical response have been published for imipramine, nortriptyline, amitriptyline, desipramine, doxepin, and protriptyline. Failure to observe a relationship has also been reported for all these drugs except protriptyline.[135]

A major problem with investigations on depression is the lack of definition of depression and the fact that more than one disease may be involved.[137,141] The diagnostic classification of the patient appears to be important in this context; consistent serum level-effect relationships have so far been established only in patients with endogenous depression.[140]

Table 15–8. Relationship Between Plasma Nortriptyline Concentration and Amelioration Score in Depressed Patients*

Nortriptyline concentration (ng/ml)	No. of patients	Amelioration score
<49	5	0.4
50 to 79	10	6.2
80 to 109	4	6.1
110 to 139	5	5.0
>140	5	1.2

*Data from Asberg, M., et al.[142]

The case for therapeutic drug concentration monitoring seems to be strongest for nortriptyline. Most careful investigations have concluded that there is a clinically useful relationship between plasma nortriptyline levels and therapeutic response but that the relationship is a curvilinear one. The therapeutic concentration range for nortriptyline is considered to be 50 to 150 ng/ml; generally, patients with lower or higher levels do not respond as well (Table 15–8).[142] This is unusual; ordinarily, the upper boundary of a therapeutic concentration range is related to the emergence of toxicity. With nortriptyline, the upper boundary reflects loss of efficacy rather than toxicity.

Amitriptyline has been studied in more than 300 patients, but the results are less consistent than for nortriptyline. In general, a minimum concentration of 80 to 120 ng/ml of total tricyclic antidepressant (i.e., amitriptyline plus nortriptyline) seems to be required for efficacy. An upper plasma level limit, above which the therapeutic effect is poor, has been suggested by some studies but not by others.[140]

More recently, Breyer-Pfaff et al.[143] reported the findings of a double-blind study in 29 depressed patients receiving amitriptyline 150 mg/day for 4 weeks. The severity of depression was assessed before treatment and after 2 and 4 weeks, and plasma levels of amitriptyline, nortriptyline, and 10-hydroxy nortriptyline were monitored weekly. Response, reflected by percent reduction in Hamilton Depression Rating Scale score, was better at steady-state amitriptyline + nortriptyline concentrations of 125 to 210 ng/ml than at lower or higher plasma levels. No influence of the 10-hydroxy metabolite of nortriptyline was discerned. The investigators concluded that "plasma level monitoring may be helpful when patients do not respond to conventional amitriptyline doses."

Several studies, involving small numbers of subjects, have suggested a relationship between imip-

ramine + desipramine concentrations, up to 250 ng/ml, and therapeutic effectiveness in patients treated with imipramine. More recently, Rigal et al.[144] monitored imipramine and desipramine levels in 51 depressed inpatients treated with imipramine 4 mg/kg per day. Combined steady-state blood levels ranged from 60 to 585 ng/ml with a mean value of 271 ng/ml. No correlation was observed between the dose of imipramine and plasma concentrations.

Consistent with earlier reports, Rigal et al. found a positive correlation between the combined levels of imipramine and desipramine and effectiveness, with a leveling off at around 250 ng/ml. They also found that the imipramine/desipramine ratio was an important parameter. Of the patients responding to imipramine, 86% had ratios between 0.4 and 1.0. Conversely, most patients with a ratio below 0.4 or above 1.0 were nonresponders.

There are also conflicting reports as to the relationship of plasma levels to effectiveness in patients treated with desipramine. For example, Simpson et al.,[145] in studying patients with depression dosed with desipramine 150 mg/day, reported that desipramine levels in plasma ranged from about 10 to > 400 ng/ml in both responders and nonresponders. The results provided no support for routine monitoring of desipramine levels.

More encouraging results were reported by Nelson et al.[146] These investigators studied the relationship between desipramine plasma concentration and antidepressant response in 30 depressed inpatients treated for 3 weeks with desipramine 100 to 300 mg/day.

Eleven of the patients were evaluated as responders. These patients had a mean desipramine level of 184 ng/ml, significantly greater than that found in nonresponders (mean value, 71 ng/ml). The plasma level that best separated responders and nonresponders was 115 ng/ml. Eight of 9 patients with levels above 115 ng/ml responded to desipramine, whereas only 3 of 22 patients with levels below 115 ng/ml responded to the drug. Ten nonresponders were converted to responders by increasing daily dosage to produce desipramine levels of 125 ng/ml or above.

More recently, these investigators evaluated desipramine plasma levels and response in elderly melancholic patients.[147] Again, desipramine levels in responders (median, 126 ng/ml) were significantly higher than those in nonresponders (median, 81 ng/ml). Among elderly patients with levels above 115 ng/ml, 4 of 5 responded, and below this level, only 2 of 13 responded. Five patients not responding during the initial 3-week trial, responded when desipramine dosage was increased and the plasma levels were above 115 ng/ml.

Other antidepressants have been studied less systematically and less extensively; more information is required before drug level monitoring can be considered.

Several studies have examined the relationship between plasma tricyclic concentrations and toxicity.[135] The common side effects of the tricyclic antidepressant correlate poorly with plasma levels. The serious CNS, respiratory, and cardiovascular toxicities of tricyclics can be related to plasma concentration but are seen only at levels far above those found with therapeutic dosage regimens. Measurement of plasma tricyclic concentrations may be useful following overdosage. Levels of 1000 ng/ml or greater have been used to define a serious overdosage.

Thousands of people in the U.S. poison themselves each year with tricyclic antidepressant drugs. Acute overdoses with antidepressants account for more than one-third of all poison-related admissions to intensive care units. Seizures, ventricular arrhythmias, and death are the most serious sequelae.

It is generally held that seizures and arrhythmias occur most frequently when the combined serum concentration of the antidepressant and its major metabolite exceeds 1000 ng/ml. It is also held that this combined level is reflected in a QRS duration of 100 msec or longer on routine electrocardiography. With this construct in mind, Boehnert and Lovejoy[148] undertook a prospective study of 49 patients presenting within 24 hours of an acute overdose of tricyclic antidepressant drugs (amitriptyline, nortriptyline, imipramine, desipramine, doxepin, and protriptyline) to determine relationships of serum drug levels, QRS duration, and the incidence of seizures and ventricular arrhythmias.

Patients were divided into two groups on the basis of QRS interval: 13 patients (Group A) had a duration of less than 100 msec and 36 patients (Group B) had a QRS duration of 100 msec or longer. There were no deaths in either group and there were no seizures or ventricular arrhythmias in Group A, but 12 patients in Group B had seizures and 5 had ventricular arrhythmias. Patients had a first seizure or arrhythmia within 6 hours of their overdose or not at all. No patient had seizures or arrhythmias more than 24 hours after ingestion.

Consistent with the more serious overdose situation in Group B, mean serum antidepressant levels were about twice as large in group B as in Group A, 1473 vs 792 ng/ml.

Although the difference in maximum serum drug levels between the groups was statistically significant, the range of values in each group was considerable. Two patients in Group A had serum levels greater than 1000 ng/ml, and 11 patients in Group B had serum levels below 1000 ng/ml. There was no statistically significant association between serum antidepressant levels and the occurrence of seizures or arrhythmias when 1000 ng/ml was used as a cutoff point.

The investigators concluded that "the fact that such a simple bedside procedure—electrocardiography—can predict the likelihood of both seizures and ventricular arrhythmias in acute tricyclic antidepressant overdose is noteworthy. The facts that the electrocardiogram is more accurate and its results are more rapidly available than serum drug measurements make it an invaluable tool in assessing the clinical risk in acute antidepressant overdose."

Some investigators strongly advocate the monitoring of serum nortriptyline or serum amitriptyline plus nortriptyline levels in selected patients during therapy; others are more cautious; still others contend that the costs of these tests outweigh their value. Burrows and co-workers concluded that until further studies have been carried out, "routine monitoring of plasma levels of tricyclic antidepressant is not warranted. The majority of patients (70 to 80%) respond satisfactorily to a standard dose of 150 mg/day of the commonly prescribed tricyclics. The cost of plasma assay is still rather expensive and the dangers of relying on a 'magical' if not inaccurate plasma level measurement, rather than clinical judgment, is still real."[149]

Gram and his colleagues advocate a different position.[140] They note that "there is a solid rationale for using drug level monitoring as a guide for dose regulation in tricyclic antidepressant treatment." They also point out that "drug level monitoring cannot replace diagnostic evaluation and clinical control of the patients but it should be considered as a significant addition to the treatment procedure in order to enhance efficacy and safety." Further investigations, better diagnostic classification and evaluation of outcome, and simpler methods of drug analysis are required before a conclusion can be reached regarding the value of serum tricyclic level monitoring.

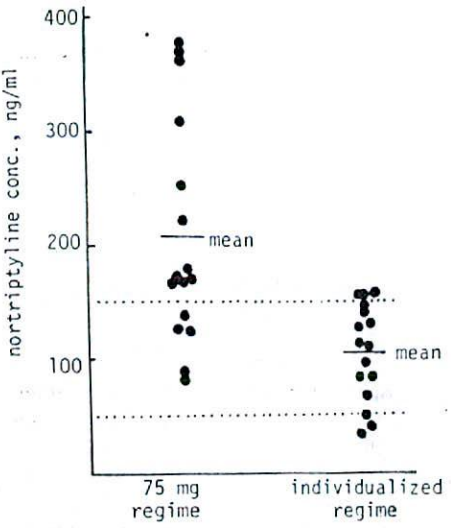

Fig. 15–7. Comparison of steady-state nortriptyline concentrations in plasma from patients who received 75 mg/day with those from patients who received an individualized dosage ranging from 20 to 90 mg/day. Horizontal lines delineate the therapeutic concentration range. (Data from Dawling, S., et al.[150])

Those who hold that there is a relationship between plasma tricyclic concentrations and efficacy strongly support efforts to optimize the initial dosage regimen in order to reduce the need for drug level monitoring and reduce the time required to achieve a desirable plasma tricyclic concentration range. An approach to predict dosage at the outset of therapy is to determine the pharmacokinetics of the drug after giving a single initial or test dose to the patient. This information is then used to calculate the daily dosage and dosage interval required to achieve a desired range of plasma drug concentrations. This approach has been used with aminoglycoside antibiotics, theophylline, and phenytoin, as well as with tricyclic antidepressants.

Success in predicting steady-state concentrations of tricyclics based on the clearance determined after a single dose has been reported for imipramine, nortriptyline, and desipramine.[138] More recently, a useful correlation has been reported between nortriptyline clearance determined after a single dose and steady-state concentrations in depressed elderly patients, ranging in age from 69 to 100 yr.[150] The predicted dosage of nortriptyline required by

individual patients to achieve steady-state plasma concentrations within the putative therapeutic range varied from 20 to 90 mg a day. Figure 15–7 compares predicted steady-state nortriptyline levels if all patients received a daily dose of 75 mg with levels actually achieved with individualized dosage.

Cooper and Simpson have proposed a much simpler method for predicting the dosage of tricyclics required to achieve a desired steady-state concentration.[151,152] This method is based on the relationship between clearance and the concentration of a drug in the plasma at a certain time after administration of a single test dose.[27,153] The 24-hr nortriptyline level after a 50-mg oral test dose accurately predicted steady-state plasma nortriptyline concentrations in human subjects ingesting 25 mg twice a day.[151] Similar success has been reported for imipramine, desipramine, and amitriptyline.[154–156] More recently, Sallee et al.[157] demonstrated that the combined plasma concentration of imipramine and desipramine 24 hr after a single 25-mg oral dose of imipramine correlates ($r = 0.92$) with steady-state imipramine + desipramine levels in children with depression receiving imipramine 3 mg/kg/day.

Methylxanthines

Caffeine, theophylline, and theobromine have been used as mild stimulants by societies through the ages. One or more of these alkaloids is found in tea, coffee, cola-flavored drinks, cocoa, and chocolate. Theobromine is rarely used as a drug today. Caffeine is widely available in the form of chewable tablets to overcome drowsiness. It is also used in the treatment of apnea in premature infants.

Theophylline and related compounds are the most important drugs in this category. Knowledge of its pharmacokinetic characteristics and the use of therapeutic drug concentration monitoring are critical factors in the resurgence of interest and use of theophylline in the U.S. for the treatment of bronchial asthma.

Theophylline. Theophylline-containing drugs include aminophylline, a 1:1 complex of theophylline and ethylenediamine containing about 80 to 85% anhydrous theophylline, oxtriphylline, a choline salt of theophylline containing 64% anhydrous theophylline, and anhydrous theophylline. Dyphylline is a different but closely related drug and is presumed to have the same mechanism of action as theophylline.

Aminophylline and oxtriphylline are more soluble than theophylline. Aminophylline is the form of theophylline used for intravenous administration. At one time it was thought that the solubility of theophylline was too low for effective oral administration. Today we recognize that theophylline is well absorbed after oral administration and the use of oral aminophylline has declined.

Theophylline competitively inhibits phosphodiesterase, the enzyme that degrades cyclic AMP. Presumably through this mechanism, theophylline relaxes smooth muscle of the bronchial airway and pulmonary blood vessels to relieve bronchospasm and increase flow rates and vital capacity.

The clinical pharmacokinetics of theophylline has been reviewed by Ogilvie.[158] Theophylline is rapidly and completely absorbed from oral solutions and conventional tablets or capsules; bioavailability problems may be encountered with prolonged-release dosage forms and rectal suppositories. Theophylline is eliminated by hepatic metabolism; less than 10% of a dose is excreted unchanged in the urine. In the neonate, theophylline is metabolized in part to caffeine; this may contribute to its efficacy in the treatment of apnea. There is evidence in children that the metabolism of theophylline is capacity-limited.

The half-life of theophylline is about 7 to 8 hr in nonsmoking, healthy adults but is considerably shorter (about 3 to 4 hr) in smokers and in children 1 to 9 years of age; these patients require higher mg/kg doses. Theophylline dosage may need to be reduced in patients with CHF or liver disease. The short half-life of theophylline in children has encouraged the widespread use of prolonged-release preparations that are given less frequently than conventional oral dosage forms.

The large variability in the dosage requirements of theophylline, its low therapeutic index and serious toxicity at excessive doses, and the good correlation between plasma theophylline levels and both efficacy and toxicity are the principal reasons that therapeutic drug concentration monitoring is recommended in certain patients.[159–161] Studies have shown that improvement of pulmonary function in asthmatic patients is related to the concentration of theophylline in the blood or plasma. For example, plasma theophylline levels of 5 μg/ml, 10 μg/ml, and 20 μg/ml were associated with average improvements in forced expiratory volume of 29%, 58%, and 85%, respectively.[162] These studies suggest that the optimal plasma theophylline con-

centration is about 10 to 15 μg/ml, on the average. Some patients, however, may benefit from plasma theophylline levels of 20 μg/ml or higher. Concentrations below 5 μg/ml are ordinarily considered subtherapeutic. Plasma theophylline levels of 20 to 35 μg/ml can cause adverse effects, which include anorexia, nausea, vomiting, agitation, tachycardia, and hypotension. It is generally believed that there is the potential for cardiac arrhythmias, seizures, and death with plasma theophylline concentrations exceeding 35 μg/ml. On the other hand, Aitken and Martin[163] have reported that serum levels were not useful in predicting life-threatening theophylline toxicity.

Children and perhaps other patients are at greater risk when theophylline is maintained in the high therapeutic plasma concentration range (i.e., 15 to 20 μg/ml). Relatively small changes in health status (e.g., fever or influenza) may decrease theophylline clearance, resulting in excessive blood levels and drug toxicity. Plasma concentrations of theophylline should be determined every 6 to 12 mo in children because clearance decreases with age between childhood and adulthood, and dosage may need to be reduced.

The value of monitoring theophylline concentration in saliva has also been investigated. The use of saliva as a substitute for serum or plasma theophylline determinations is usually not recommended, however, because a relatively high degree of intersubject variability in serum-to-saliva concentration ratio has been reported and, in some patients, the ratio does not remain constant. Contrary to this view, Vaughan et al.[164] have suggested that measuring theophylline concentration in passively absorbed saliva is useful for determining bioavailability of prolonged-release theophylline products in children.

Guidelines for dosing children and other patients with theophylline are available.[159,161] Koup and associates described a pharmacokinetic method for determining dosage requirements in individual patients to achieve a desired steady-state concentration of theophylline.[165] Asthmatic children were given 1 dose of theophylline (5 mg/kg); 6 hr later serum theophylline concentration was determined and used with a clearance nomogram to predict the dosage regimen needed to achieve a steady-state theophylline level of 10 μg/ml.[166] Individual daily dosage requirements ranged from 10 to 32 mg/kg. These individualized doses resulted in an average concentration of 12.0 μg/ml. Individual steady-state serum theophylline concentrations ranged from 6.2 to 16.0 μg/ml. This approach appears to be a safe and effective method for initiating theophylline dosage.

The widespread interest in monitoring theophylline therapy has prompted two manufacturers to market kits to measure serum levels in a physician's office in as little as 15 minutes. One kit, the Seralyzer-ARIS Theophylline Test, is available from Ames and the other, called Accu-Level, is available from Syntex. Unlike the Ames kit, the Accu-Level test does not require an analytical instrument and can use whole blood, eliminating the need for centrifugation and dilution. Both kits have been described in the Medical Letter.[167] The accuracy and precision of each kit has been evaluated by Vaughan et al.[168,169] Both methods are considered useful.

CONCLUSIONS

Therapeutic drug concentration monitoring as a guide to drug therapy is a small but definite part of clinical pharmacokinetics. Twenty years ago many of us hoped that it would grow in importance as our understanding of drug effects improved and better methods for drug and metabolite analysis were developed. This has not been the case.

In 1985, Sjoqvist[170] observed that "data supporting the clinical value of measuring plasma drug levels are still limited and it is not uncommon that therapeutic drug monitoring leads to 'treatment' of the plasma level rather than the patient."

In 1988, Spector et al.[171] announced that the time had come to validate the 'intuitive logic' that underlies therapeutic drug monitoring. They called for controlled, prospective clinical trials designed to test and prove the practical utility of therapeutic drug monitoring and thereby define the specific conditions and drugs for which it may prove beneficial. "The clinical utility of the target concentration strategy needs to be confirmed or the concept rejected if found useless."

In 1989, McInnes[172] observed that the value of therapeutic drug monitoring to the practicing physician is a hypothesis in need of testing. He asks that "in the light of all the uncertainties, why is therapeutic drug monitoring so widely advocated?" and concludes that "too much enthusiasm for therapeutic drug monitoring as an essential component of rational prescribing confront the practicing physician. Too little effort has gone into testing the hypothesis."

Even today, however, therapeutic drug monitoring still has its ardent defenders. Vozeh[173] evaluated the cost-effectiveness of therapeutic drug monitoring and concluded that although there is little direct evidence concerning the cost-benefit of therapeutic drug monitoring and prospective evaluation is needed, "there are sufficient data to conclude that the cost-benefit ratio can be improved by performing therapeutic drug monitoring with the appropriate expertise."

Setting this debate aside, it is undeniable that there is a need today for individualized approaches to drug therapy, be they based on serum levels, clinical response, or laboratory tests. There is considerable room for improvement in how we use the drugs available today and those that will be available in the years that lie ahead.

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