An overview of therapeutic drug monitoring principles[1]

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Recent technological advances allow determination of anticonvulsant blood levels. Consequently, the principles of pharmacokinetics can be applied in managing patients with seizures. We review these principles as well as those of therapeutic drug monitoring for the control of antiepileptic drug levels.

Index terms: Anticonvulsants • Epilepsy • Pharmacology, clinical

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Therapeutic drug monitoring (TDM) is a multidisciplinary endeavor encompassing specialities such as clinical pharmacology, clinical pathology, clinical chemistry, toxicology, analytical chemistry, and medicine. Interdisciplinary scientific communication, however, has been suboptimal since journals tend to be narrowly discipline-oriented rather than subject-oriented. Yet workers now require broad-based knowledge from a wide variety of disciplines in order to optimize patient care.

Both clinicians and pharmacologists have attempted to determine why a fixed drug dosage is therapeutically effective in some individuals but not in others. For years, appropriate dosage regimens were established empirically, but modern analytic techniques have provided an alternative. Correlation of serum or plasma drug concentrations and, by inference, tissue concentrations with the observed clinical effect of a given agent has provided new therapeutic insights. Historically, measurement of serum concentrations was a function of the clinical pharmacology labora-

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tory, but increasing demand for such measurements on a routine basis has exceeded the capacity of many research laboratories; consequently, drug analysis is performed routinely in clinical chemistry laboratories. Increased demand for this procedure has elevated TDM into a new scientific discipline.

New analytical techniques are beginning to clarify the interrelationships between drug dose and pharmacological effect. The desired pharmacological effect of many drugs is achieved only after a specific plasma concentration is attained, and there is usually an optimal plasma concentration range for successful drug therapy. Above this range, patients may experience undesirable side effects. Below this range, patients may not gain relief from the disease or symptom. Rapid advances in clinical pharmacology during the past decade are directly attributable to TDM, which, in turn, depends upon rapid advancement in the technology for measuring drug compounds.[1–5]

Therapeutic drug monitoring has been associated with clinical laboratory medicine since 1927 when Wuth demonstrated the value of monitoring serum bromide concentrations to differentiate bromide-induced psychotic behavior from psychotic behavior attributable to organic causes. During World War II, the search for anti-malarial compounds resulted in improved analytic instrumentation, improved techniques for drug quantitation, and new insights into the relationship between drug concentration and therapeutic effectiveness. The first studies correlating plasma drug concentrations with therapeutic efficacy were published in the late 1950s and early 1960s.

Therapeutic drug monitoring did not become widespread until the late 1960s. Gas-liquid chromatography (GLC) provided a method of rapidly separating and quantitating individual drugs within a given class. By the early 1970s GLC analysis of various therapeutically monitored agents was routine in many clinical chemistry laboratories. A major disadvantage of GLC had been the complexity of the instrumentation, which necessitated a highly trained and skilled analyst. The development of the nitrogen-phosphorus detector and capillary GLC (gas-liquid chromatography) columns has increased the sensitivity of the instruments so much that drug analyses can be performed routinely on microvolumes of plasma.[6]

Making TDM available to all laboratories and physicians required simple technology that could be performed by a technician without special training. Consequently, the homogeneous enzyme immunoassay system (EMIT), which can perform assays on less than 40 μL of serum, was developed. The major advantages of this system are its microcapability and accuracy and the rapidity and ease of operation of the assays. More recently, substrate-labeled fluorescent immunoassays (SLFIA) and fluorescence polarization immunoassays (FPI) for the rapid quantitation of drugs have become available.[7]

The development of radioimmunoassay (RIA) techniques also permitted quantitation of drug concentrations in micro-volumes of serum. Unfortunately, the complexity of the technique and the unavailability of radioimmunoassays for a wide variety of drugs prevented its use for routine drug monitoring.

Many drugs must be therapeutically monitored for which antibodies are not available. High pressure liquid chromatography (HPLC) is the most promising and practical method of monitoring these agents. In the last decade, the development of HPLC has provided laboratories with a system, which like the homogeneous enzyme immunoassay system, is capable of processing microsamples (100 μL), is rapid and specific, and uses instrumentation that can be operated without special training. In addition, HPLC can be adapted to simultaneously quantitate a large variety of drugs and their active metabolites. This technique permits simultaneous drug analysis and is a valuable tool for establishing correlations between drug and drug metabolite concentrations in biological fluids.[7,8]

Therapeutic drug monitoring, however, is not a panacea for all problems associated with drug therapy. Specific clinical criteria for monitoring drug concentrations are presented in *Table 1*. Therapeutic drug monitoring is most applicable when the drug in question has a narrow therapeutic range, is used continuously, has potentially toxic side effects if overdosed, and has minimal therapeutic effects if underdosed. Both clinical and molecular studies of the pharmacologic profiles of a wide variety of drugs have demonstrated that a much better correlation exists between the observed clinical effects of a drug and its plasma concentration than between the clinical effect and total daily drug dosage. With this in mind, TDM can be used for the following purposes:

To recognize non-compliance. Many patients, especially those with chronic disease requiring pro-

longed therapy, tend not to take their medications as prescribed. Moreover, patients with a chronic disease that does not continually cause pain or other unusual discomfort (e.g., the epilepsies, asthma, or hypertension) may easily neglect their medicine. Such non-compliance eventually exacerbates the disorder. Studies[1–5] demonstrate that patient non-compliance is a major reason for treatment failure.

To compensate for individual variations in drug utilization patterns. If plasma concentrations following a specific dosage are analyzed in a large patient population, the distribution of drug levels at steady state will be gaussian. Most patients will have levels within the range expected from a dosage based on body weight, but those who are genetically either "fast" or "slow" drug metabolizers will have levels at the extreme ends of the curve. Fast drug metabolizers require significantly higher doses to achieve the same plasma concentrations and desired therapeutic effect. Slow drug metabolizers experience side effects from standard therapeutic doses of the drugs; therefore, optimal drug levels can be attained with dosages well below the standard regimen.[1–5,9,10]

To compensate for altered drug utilization associated with various disease states. Patients on long-term drug therapy may become acutely ill and need additional therapeutic agents. Drug interactions may then cause these patients to respond unexpectedly to a fixed dosage of medication. Acute or chronic uremia can dramatically decrease elimination of a drug primarily dependent on urinary excretion, and renal failure can alter the binding of many drugs to albumin. In both situations, the ratio of free drug to total drug may increase to the point where free drug concentrations are high enough to produce a clinically evident drug response although the total serum drug concentrations are often below the optimal therapeutic range. Moreover, free drug levels can rise into the toxic range, whereas total drug concentrations remain within or even below the usual ranges.[1–5,9,10]

Hepatic disease can extensively alter a given therapeutic response by impairing a patient's ability to metabolize drugs. Most drugs depend on liver detoxification for conversion to water-soluble products, which are easily eliminated from the body. Thus, a precipitous rise in parent drug concentrations can occur as the drug (which normally would have been metabolized by the liver and then eliminated from the system) accumulates.

Table 1. Indications for monitoring plasma drug levels

1. The drug has a narrow, well-defined therapeutic range.
2. Noncompliance is suspected.
3. Desired therapeutic effect is not achieved, or symptoms of toxicity are observed.
4. Large intra-individual variations occur in drug utilization or metabolism.
5. Drug utilization is altered as a consequence of secondary disease or changing physiological state.
6. Drug interaction is suspected.
7. Medico-legal verification of treatment is needed.
8. Plasma concentrations associated with optimal response must be defined.

To adjust therapeutic drug regimens to compensate for changing physiologic states. Normal alterations in physiologic state also change drug utilization patterns. Therapeutic drug monitoring is crucial to successful adjustment of dosage regimens in pregnancy, puberty, and old age.

Recent studies have shown that decreased drug absorption during pregnancy is associated with a decrease in serum phenytoin concentration and exacerbation of seizures in epileptic gravidas. The use of TDM from the onset of pregnancy, with appropriate dosage regulation to maintain therapeutic drug concentrations, significantly decreases the number of seizures, thus decreasing potential harm to the fetus.[11–13]

Normal maturation involves many physiologic changes that can dramatically alter drug utilization. Although the rate of drug disposition in children is increased, the optimal drug concentration necessary to produce the desired therapeutic response is similar to that observed in adults. Therefore, because of faster drug clearance in children, larger doses (in mg/kg) must be prescribed to achieve and maintain optimal drug concentrations. Complex changes in drug utilization patterns occur in the weeks following birth. Older children require almost twice as much drug per body-weight as an adult to achieve the same therapeutic concentration. By early pubescence, however, the conversion to adult patterns is complete. These changes usually occur between the ages of 10 and 13, appearing earlier in girls than in boys. Therefore, medication given over long time periods must be administered carefully; blood level determinations must be frequent. Failure to adjust the child's therapeutic regimen to compensate for the associated physi-

ologic changes may culminate in drug toxicity.[11–13]

As maturation continues and normal physiologic functions decline, so does the ability to bind drugs to plasma protein. Geriatric patients often exhibit reduced rates of drug elimination, thereby requiring reduced drug dosages. Geriatric patients may have total drug plasma concentrations within the optimal therapeutic range, but elevated free drug concentrations capable of producing adverse side effects. Clinical signs of drug intoxication in the elderly often present as lethargy and confusion, and TDM provides a means of distinguishing drug-induced confusion from organic deterioration.[7,11–13]

To identify baseline concentrations associated with optimal therapeutic regimen. After a patient has undergone a strenuous work-up and an appropriate therapeutic regimen has been defined, the physician can establish a baseline drug concentration at which the patient responds well. Should the patient return in the future with uncontrolled symptoms, the physician can rapidly determine whether he has been compliant or whether a different disease state has altered the pharmacologic response to the drug.

Numerous factors, including individual differences in drug metabolism and excretion, age, sex, patient compliance, disease, and drug interactions (particularly during multiple drug therapy), regulate the disposition pattern of a drug within the patient. The disposition pattern, in turn, regulates the plasma concentration and thus the amount of drug available to interact with a receptor. The therapeutic response observed in the patient depends on all these processes, and is directly related to the drug concentration in that patient. Interactions between all factors influencing drug disposition account for the broad interpatient variability in plasma concentrations following either single or multiple drug dosages. Individual response to a given drug dosage remains constant, however, because the factors which alter drug utilization within the individual are relatively fixed.

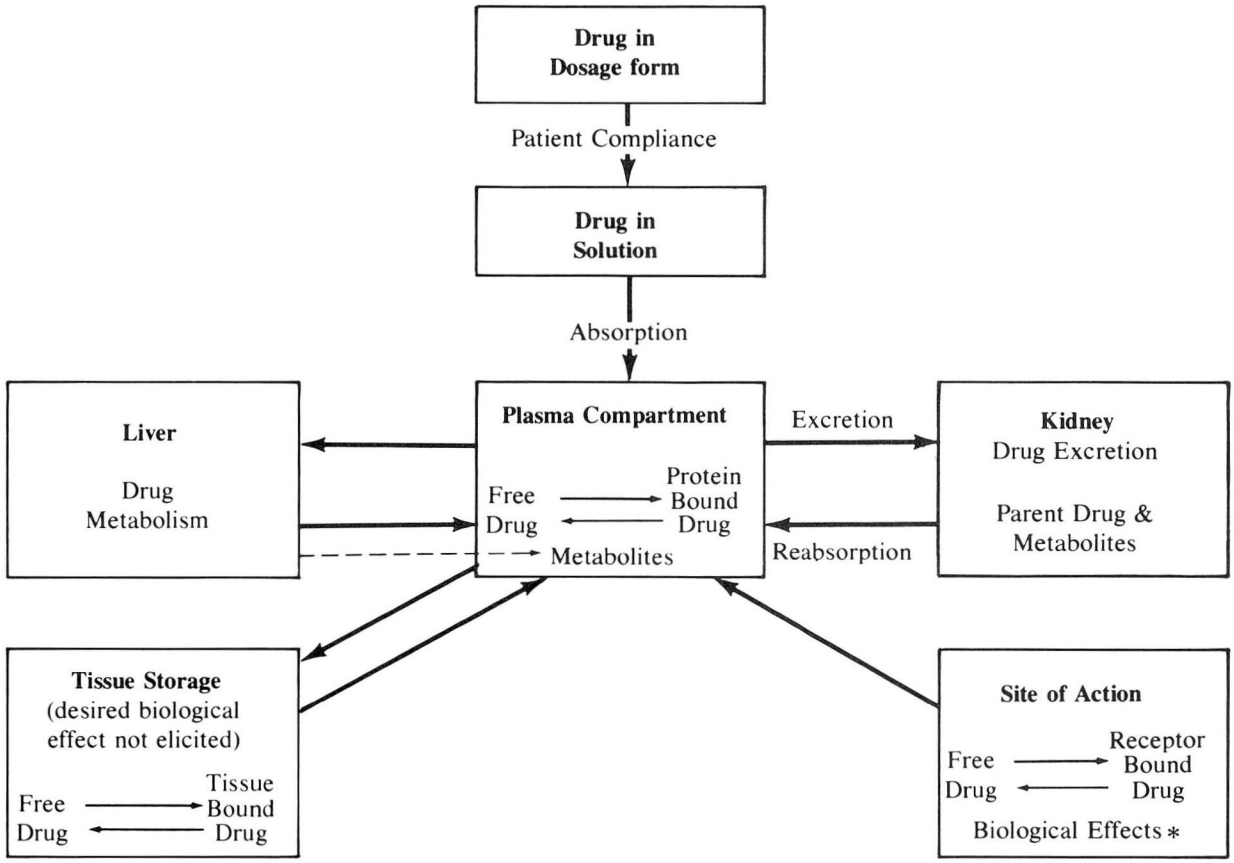
Generally, interindividual variations in response, as demonstrated by the clinical response of a large population to a fixed drug dosage, reflect the relationship between total daily dose and plasma concentration rather than the relationship between plasma concentration and intensity of response. In other words, the probability of achieving a given plasma concentration from a given drug dose is much less than the probability of obtaining a specific biological effect from a given plasma concentration. Consequently, fixed dosages produce marked therapeutic response variations within a population. When a standard drug dosage is prescribed for a large patient population, the desired therapeutic effect will be achieved in some patients, no therapeutic effect will occur in others (usually associated with low plasma levels), and toxicity (usually associated with elevated plasma levels) will be evident in still others.[1–5,11–13]

Pharmacodynamics: site and mechanism of drug action

The biological effect achieved following a given drug dose is a direct consequence of the formation of reversible bonds between the drug and the tissue receptors controlling a particular response. For most drugs, the intensity and duration of a given pharmacological effect are proportional to drug concentration at the receptor site.[4,14] The exact mechanism of receptor interactions, however, remains unclear. A drug can only produce the desired biological effect when it reaches and interacts with the receptors regulating a specific reponse. In addition, disease, age, sex, compliance, drug interactions, and individual differences in drug metabolism and excretion contribute to different responses amongst the patient population. *Figure 1* depicts factors which can alter drug concentration at a given receptor site. Titration of drug doses via TDM is the most precise method for achieving therapeutic plasma concentrations, thereby indirectly influencing concentration at receptor sites (see below) and reducing intra-individual variations in response.

Any drug may increase, decrease, or return to normal the physiologic function of tissues, organs, or physiologic systems. The biological effect following administration of a drug is the result of a drug-induced change involving some physiologic or biochemical process. Such effects can only be measured and expressed by the alteration of a specific function or process. A drug's pharmacodynamic activity may return a function or physiologic process from an abnormal to a normal level of activity, or it may prevent deviation from the normal physiologic state.

The intensity of a pharmacologic effect for most drugs tends to be proportional to the drug present in extracellular fluid, which can enter tissues and interact with specific receptors to elicit a biological effect. For example, antiepileptic drugs are thought to prevent seizures by binding



Absorption

Drug must be formulated in a manner which assures bioavailability for absorption.

Metabolism

Drug converted to a more soluble compound which may be biologically active or inactive. Metabolism can also occur in other tissues.

Excretion

Usually more water soluble drug metabolites are excreted in urine. Also drug excretion can occur via bile, feces, saliva and expired air.

Tissue Storage

Distribution of drug to sites where the desired biological effect is not elicited. Undesirable effects may be elicited by drug interaction with a specific physiological system.

Site of Action

Free drug binds to receptor to elicit a biological effect (response). Number & type of receptors to which drug is bound determines the intensity and duration of the desired and undesired effects.

Fig. 1. Factors altering drug concentration ultimately achieved and maintained at a given receptor site.

to neural membranes or by altering neurotransmitter release. Alteration of these functions is thought to reduce or limit the spread of excessive electrical activity responsible for precipitating a clinical seizure.

After absorption, a drug is distributed between the plasma and various tissue compartments (*Fig. 1*). Since many drugs are partially bound to plasma proteins, an equilibrium exists between the concentration of protein-bound drug and the free drug concentration in plasma water. The drug concentration in plasma water is in equilibrium with that of extracellular water. Only free drug can cross the various lipoprotein membranes that surround the receptor sites. Receptor site drug concentrations cannot be directly monitored in vivo, but total plasma drug concentrations reflect the equilibrium between tissue, extracellular fluid, and plasma water drug concentrations, whereas plasma free drug levels reflect levels in the extracellular space. The latter, assessed in the TDM laboratory by measuring the free drug concentration, is thus an indirect measure of drug concentration at the *site of action*, that is, the location where a given drug initiates the events culminating in a specific biological effect. Such an effect may be elicited by direct drug interaction with a receptor that controls a specific function or by alteration of the physiologic process that regulates that function.

The *mechanism of action* of a drug refers to the actual biochemical or physical process that initiates a biological response at a specific site. This process is dependent upon the chemical interaction of the drugs with a functionally viable component of some physiologic system. The exact molecular mechanism remains obscure, but drugs are thought to bind with intracellular macromolecular receptors by ionic and hydrogen bonds and van der Waals forces. Such a reversible combination forms a drug-receptor complex of sufficient stability to alter the physiologic response of the target system, consequently producing the observed pharmacologic effect.[4,5,14]

Pharmacokinetics

Anyone using routine TDM must remember that the plasma concentration achieved and maintained after administration of a fixed drug dosage is a direct consequence of the interactions of a wide variety of interrelated processes (*Fig. 1*), including drug absorption, distribution, metabolism, excretion, and the physiologic status of the patient. The study of these interrelationships forms the basis of pharmacokinetics.

Pharmacokinetics is the study of the time-course of drug and metabolite levels in various fluids, tissues, and excreta of the body. Pharmacokinetics employs mathematical models to predict the distribution and excretion patterns of drugs, usually at steady-state concentrations, in response to a given dosage regimen. The theoretical limitations of the models must be recognized, however, when using clinical pharmacokinetics to treat a patient on a specific drug regimen. For example, many models do not take into account multiple-drug therapy or the clinical status of the patient. Interactions between drugs can alter the kinetics of each and affect plasma drug concentrations as well. Therefore, unless specific clinical data are available for a given patient, these models should serve only as a general guideline.[2–5]

Techniques for monitoring drug levels in biological fluids allow correlation of a given mg/kg dosage of drug with the observed plasma concentration and clinical response in large patient populations. The fundamental assumption of these studies is that the patient is at steady state, i.e., the intake of a drug has been constant over a period of time, and drug elimination, as reflected in rates of drug metabolism and excretion, is also constant. In a number of computer programs, plasma concentration data with respect to time are used to calculate the drug dosage necessary to achieve a given plasma drug concentration in a specific patient. Unfortunately, these programs and the information derived from them are not yet widely available to clinical chemistry laboratories or practicing clinicians.

Clinical application of these programs does not require a detailed knowledge of pharmacokinetics.[2] However, knowledge of the terminology and fundamental principles is essential:

First-order kinetics: A process associated with drug utilization (clearance) exhibits first-order kinetics when there is a linear relationship between plasma drug concentration and total daily dose (mg/kg). *Figure 2, curve A* shows that an increase in drug dose would be expected to result in a proportionate increase in plasma drug concentration.

Zero-order kinetics: When the rate of a process is independent of concentration, it is said to follow zero-order kinetics. Zero-order kinetics becomes apparent when enzyme or transport mechanisms become saturated. Although plotting of drug plasma concentration versus total daily dose (mg/kg) initially yields an apparently straight line indicative of first-order kinetics, a sharp upward curve is seen as the saturation point is reached. Changes in the rates of drug clearance beyond the saturation point, as represented by the disproportionate increase in plasma drug concentration after a given dosage increment, are the hallmark of zero-order kinetics (*Fig. 2, curve B*).

Fortunately, in clinical practice, only a few drugs exhibit zero-order kinetics. For most drugs, plasma concentrations achieved at therapeutic dosages are low relative to the concentration necessary to saturate the particular system involved. Therefore, first-order kinetics is observed throughout the therapeutic range. There are notable exceptions to this rule, however, since both phenytoin and aspirin exhibit saturation kinetics near the upper limits of the therapeutic range. For any drug that exhibits zero-order kinetics, a very small dosage increment may result in a clinically significant elevation of plasma concentrations. Even though the initial dose-response curve may appear linear in drugs with zero-order kinetics, drug clearance is altered throughout the dosage range and at all plasma concentrations and does not parallel the kinetics observed in a first-order relationship.

Drug half-life: Drug half-life, also referred to as the elimination half-time $t_{1/2}$, is the time required for elimination of half the concentration

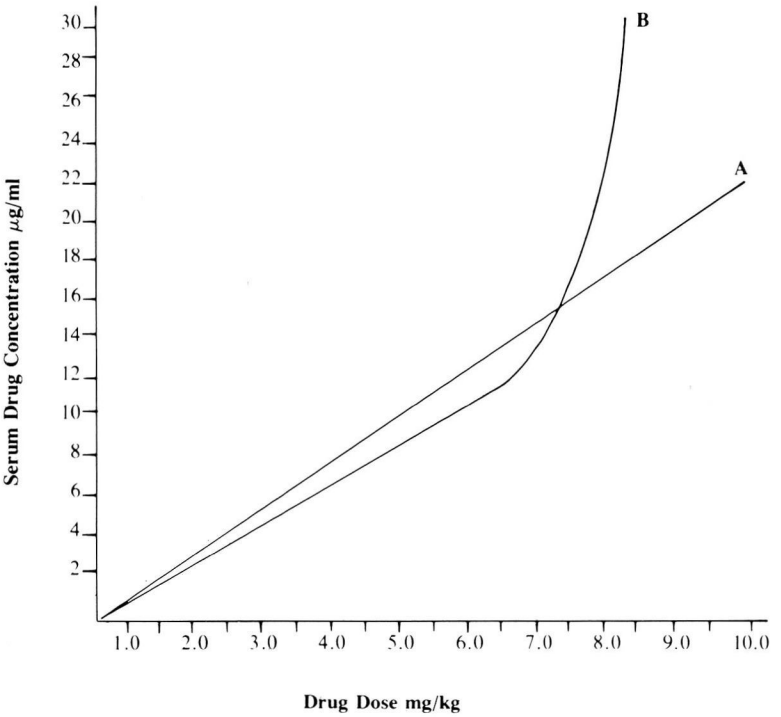


Fig. 2. Dose-response curves. *A*, first-order kinetics (linear), and *B*, zero-order kinetics (non-linear or saturation).

of a drug present in the system, provided no additional drug is administered. For example, if the concentration of phenytoin ($t_{1/2}$ = 24 hr) were 20 μg/mL, the time required to clear the drug to a concentration of 10 μg/mL would be 24 hours, provided no additional doses of the drug had been given. Drug half-life reflects the individual rates of the various processes regulating drug clearance. Rates of drug metabolism and excretion are the primary determinants of drug half-life in any patient (*Fig. 3*).

Fate of a single drug dose: After administration

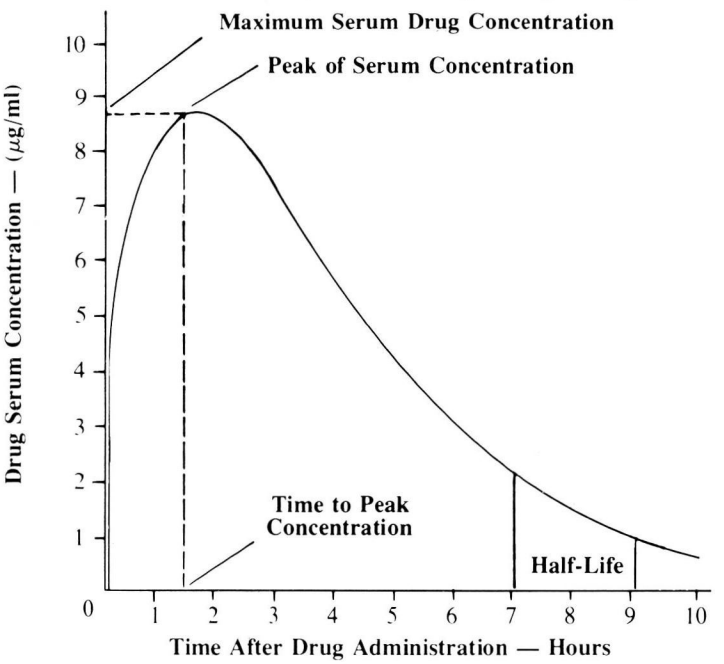


Fig. 3. Dose-response curve after oral administration of a single dose of hypothetical drug. (Abstracted by permission of the *New England Journal of Medicine*, 1974; **291:**234)

of a single drug dose, a peak plasma concentration is reached when the absorption phase is almost complete. The plasma concentration then begins to decline, even as the drug continues to be absorbed. The rate of decline in plasma concentration is dependent upon the rates of absorption, metabolism, and excretion of the drug. Once the absorption phase is complete, the rate of decline in plasma concentration is a reflection of the clearance (elimination) rate, which is the sum of the rates of excretion and metabolism of the drug. After the absorption phase, the half-life can be determined by measuring the decline in plasma concentration over fixed time intervals (*Fig. 3*).

Steady State: When long-term oral therapy is initiated, the drug will continue to accumulate within the body until the rate of clearance, which comprises all tissue distribution, metabolic, and excretion processes involved in drug disposition, equals the rate of administration. When an equilibrium between drug clearance and intake is achieved, the system is said to be at a *steady state*, i.e., the amount of drug ingested over a 24-hour period is equal to the amount of drug eliminated in the same period. Over time, body and plasma drug concentrations will increase exponentially until they reach a steady state or plateau. Seven half-lives of drug administration are required before true steady state concentration is achieved and stabilized. Steady state processes are, however, 97% complete within five half-lives, and, as a practical rule, five to six times the half-life of any drug is required to achieve a steady state. For example, phenytoin, which has a half-life of 24 hours, requires a period of 24 × 5.5 or 132 hours (five to six days) to achieve a steady state. In contrast, drugs such as primidone or valproate, which usually have a half-life of six to eight hours, require only 33–44 hours to reach a steady state.

The same principles which govern the gradual accumulation of a drug to a steady state also apply when drug therapy is discontinued. For instance, if plasma phenytoin is at a steady state concentration, and drug administration is stopped, a period of five to six days, or five to six half-lives, will elapse before the drug is completely eliminated. Thus drugs with prolonged half-lives can still be detected in plasma for three to four weeks after administration of the last dose. For example, phenobarbital, with a half-life of four days, requires 22 days for complete elimination. Bromides, with a half-life of 12 days, require 66 days for complete elimination.

Plasma concentrations of drugs with first-order kinetics during the steady state are linearly related to dose. For any change of dosage, after a steady state has been achieved, the principles regulating the time required to achieve a new steady state still apply. For example, if the maintenance dose of a drug were doubled, the new steady-state concentration would not double until the completion of five to six half-lives. If a plasma drug concentration is determined before achievement of a steady state, for example, after two half-lives, it will not reflect the true steady-state concentration of the drug. For drugs exhibiting zero-order kinetics, half-lives increase after the saturation point is reached. Thus, after saturation, it will still take five to six half-lives to reach steady state, but the half-life at saturation is prolonged. This is why a phenytoin level of 35-40 μg/mL will not drop to 17–20 μg/mL after 24 hours. At these higher levels, saturation of metabolic processes occurs, resulting in a half-life longer than 24 hours.

The full therapeutic effect from a given dose is not achieved until steady-state concentrations are reached. Therefore, before a given dosage regimen is considered to have failed, the clinician should ascertain that steady-state concentrations have indeed been achieved.

Factors that alter individual drug disposition patterns *(Table 2)*

Patient noncompliance

Studies have revealed that over 60% of all patients do not take their medications in the manner prescribed.[1–5] Patient noncompliance is the most common cause of suboptimal drug concentrations and consequent failure to achieve the desired therapeutic response. Whenever a patient presents with consistently low plasma drug concentrations, noncompliance should be considered the probable cause. Noncompliance can usually be demonstrated by careful supervision of the patient's daily drug intake over a specified time interval (usually five half-lives of the drug) with routine monitoring of serum drug concentrations at appropriate intervals. If serum drug concentration increases progressively over the time interval selected, the patient has been noncompliant.

Administration of the recommended or aver-

age total daily dose of a given drug without considering the numerous factors that alter drug disposition in each patient can also lead to consistently low serum drug concentrations. Thus, if serum concentrations remain low under supervised intake, other causes such as drug malabsorption or rapid drug metabolism should be suspected. Finally, failure to individualize drug therapy (*physician noncompliance*) is often responsible for suboptimal drug concentrations.

Drug absorption: Some patients receiving appropriate drug doses will have consistently low plasma drug concentrations. Generally, these patients are either noncompliant or fast drug metabolizers. Before classifying someone as a fast metabolizer, the physician must evaluate the patient's ability to absorb the drug. Entry of drugs into the general circulation after parenteral administration is generally rapid and circumvents the problems associated with oral administration; however, most drugs are administered orally. The type of drug preparation, drug solubility, concomitant administration of other drugs, whether the drug is taken with meals, and the presence of diarrhea or constipation can alter the amount of drug absorbed from the gastrointestinal tract after a single oral dose.

Malabsorption of an orally administered drug can often be confirmed by measuring serial plasma drug concentrations at given time intervals after parenteral administration of the prescribed dose. If altered absorption is present, maximum plasma concentrations and observed drug half-life following the IV dose will be significantly higher than those achieved after the same dose administered orally. Conversely, if the patient is a fast drug metabolizer, plasma concentrations achieved or the observed half-life will not differ significantly regardless of the route of administration.

Drug-plasma protein binding: Upon entering the systemic circulation, any protein-bound drug will bind to plasma proteins, and an equilibrium between free and bound drug will be established. *Bound drug* is that portion of a drug bound to plasma proteins. Bound drug cannot cross cell membranes and consequently exerts no biological effect. Only the unbound or *free* drug dissolved in the plasma water can be transported across biological membranes to interact with specific receptors and elicit a biological response. Each drug has its own characteristic protein-binding pattern, which depends on its physical and chemical properties. In general, acidic drugs are bound primarily to albumin, and basic drugs to globulins, particularly alpha-1-acid glycoprotein.

Table 2. Factors influencing interpretation of assay data or therapeutic drug monitoring

Patient compliance, including dosage error and wrong medication
Absorption via route of administration
Drug distribution
Biotransformation
Excretion
Genetic variability
Acute or chronic disease
Drug interactions
Drug tolerance
Inappropriate drug effects

A drug may be either tightly or loosely bound, as determined by its affinity for plasma proteins. A weakly bound drug can be displaced by another drug with greater affinity for plasma protein-binding sites. Protein-binding of a drug also depends on the physical characteristics of plasma proteins. Tightly bound drugs will not be displaced, but a weakly bound drug may be displaced quite rapidly from its protein-binding sites by elevated free fatty acids or by another drug. Even though the total serum drug concentration may remain unchanged, displacement of a drug from its plasma protein-binding site can elevate free drug concentrations, resulting in clinical toxicity.

Certain disease states can significantly alter drug protein-binding. For example, uremic patients cannot completely bind drugs to plasma proteins. In the case of phenytoin, uremic patients range from those who can bind none to those who can bind only 60%–70% of the phenytoin present in plasma. In a patient lacking the capacity to bind phenytoin (i.e., those whose phenytoin is 100% free), concentrations of 1–2 μg/mL would result in clinical effects equivalent to 10–20 μg/mL in persons whose phenytoin is bound normally (i.e., 10% free), and plasma concentrations above 2.5–3.0 μg/mL would result in phenytoin toxicity. Altered drug protein-binding requires careful monitoring of all drugs administered in patients with abnormal renal function.[1–5, 9–15]

In patients who present with either clinical toxicity or a nontherapeutic response, when total plasma concentrations are known to be optimal, altered protein-binding should be considered. Until recently, direct determination of protein-binding was a time-consuming, tedious proce-

dure. Since only free drug crosses into the saliva, the protein-binding status of a patient can be assessed indirectly by measuring salivary drug concentrations. Nevertheless, caution is indicated. Salivary levels are a good indicator of free drug levels for any drug that has an ionization constant (pK_a) signficantly different from the pH of plasma, e.g., phenytoin. However, for drugs with a pK_a similar to plasma pH, e.g., phenobarbital, salivary concentrations will not reflect true free drug concentrations. In addition, salivary drug levels will not reflect the actual free concentration of drugs actively transported into the saliva. Rapid ultrafiltration systems, which directly assess free plasma drug concentrations, circumvent this problem and should enhance our ability to identify patients who cannot bind drugs to plasma proteins normally.

Drug metabolism: Any foreign compound that enters the body must be eliminated. As one proceeds up the phylogenetic scale from fish to man, drug elimination mechanisms become more complex. The body is increasingly able to alter foreign substances into compounds which are more water-soluble and thus more readily excreted. The liver's ability to metabolize drugs probably evolved as a mechanism for detoxifying poisonous substances ingested with food.

The drug-metabolizing enzymes of the liver interact with a wide variety of chemical structures. Metabolites of many drugs are conjugated within the liver to either glucuronic acid, amino acids, or sulfates, thus increasing water solubility even more, and, consequently, the rate of renal excretion. For example, p-hydroxyphentoin, the major metabolite of phenytoin, is conjugated with glucuronic acid, which increases its water solubility almost 100 times.

Most drug metabolism occurs within the microsomal fraction of the hepatocyte, which also metabolizes endogenous steroids. The microsomal enzyme systems do not recognize specific drugs; rather, they act upon classes of compounds with similar structures. The same enzyme responsible for the hydroxylation of phenytoin also hydroxylates many other drugs containing an appropriate phenyl ring. Thus phenytoin administered simultaneously with one of these drugs may significantly alter drug concentrations as a direct consequence of competition for metabolic sites. Clinically, one would anticipate higher serum concentrations of the drug with the least affinity for the enzyme. Phenytoin has a very low affinity for microsomal enzymes. Administration of a drug with a greater affinity for the enzyme than phenytoin will decrease phenytoin's rate of metabolism, thus elevating plasma phenytoin concentrations. Not all compounds, however, are metabolized at the same site. An individual can be a fast metabolizer of one group of compounds and metabolize others normally. Likewise, one compound may displace phenytoin from its metabolic site, whereas another substance will have no effect.

The hepatic microsomal system can be induced to metabolize drugs at a faster rate. As increasing doses of drug are administered, the body synthesizes new proteins, in the form of enzymes, to metabolize that drug. Drug-metabolizing enzymatic systems do not necessarily increase their activity with every dosage increment or with the addition of another drug to the patient's regimen. There is a maximum rate at which protein synthesis can occur. Thus, if a patient has been regularly receiving a drug with known enzyme-induction properties, a second drug of similar structure added to the patient's therapeutic regimen will not necessarily markedly increase the rate of metabolism of both drugs.

Genetic factors are major determinants in a patient's ability to metabolize drugs.[9–15] Individuals of various ethnic origins and certain families metabolize drugs, e.g., phenytoin or isoniazid, at a faster or slower rate than the general population. A fast drug metabolizer will require a larger daily dose (mg/kg) than a normal individual to achieve the same serum concentration. Conversely, a slow drug metabolizer given standard drug dosages will invariably exhibit symptoms of toxicity.

Absolute identification of fast and slow drug metabolizers depends upon quantitative identification of urinary drug-metabolite excretion profiles as well as on serial determination of plasma drug concentrations. Generally, slow metabolizers will have significantly higher plasma drug concentrations than those in the general population receiving the same mg/kg/day dosage. Consistently high plasma concentrations on normal or low drug doses suggest slow drug metabolism, although a drug interaction or disease process blocking drug metabolism will also result in elevated plasma concentrations. On the other hand, fast drug metabolizers usually exhibit consistently low plasma concentrations on standard dosage regimens. Since plasma drug levels in noncompliant patients mimic those observed in fast metabolizers, noncompliant patients are sometimes

mistaken for fast metabolizers. Use of plasma drug concentrations alone to identify fast and slow metabolizers can therefore be misleading. Urinary excretion patterns help to clarify whether plasma drug levels are due to metabolic alterations, non-compliance, or another problem.

Generally, drugs are metabolized from pharmacologically active agents to inactive products, incapable of eliciting a given therapeutic response. For example, the addition of sodium valproate to the regimen of a patent receiving phenytoin may markedly decrease total phenytoin concentrations. This decrease is a direct consequence of the displacement of phenytoin from its plasma protein-binding sites. The displaced phenytoin is rapidly converted to its inactive metabolite: p-hydroxyphenytoin. The observed fall in total phenytoin levels indicates an altered rate of phenytoin disposition. Most analytical techniques for routine therapeutic drug monitoring measure the parent compound and not drug metabolites. There are exceptions: some organic metabolites have a greater biological activity than the parent compound. For example, diazepam is rapidly metabolized to desmethyldiazepam, the most active antianxiety agent of the diazepam metabolites.[9] Generally, when a compound has a less polar active metabolite, the half-life of the active metabolite is significantly longer than that of the parent compound. Such is the case with procainamide and *N*-acetylprocainamide (NAPA). The half-life of procainamide is three to four hours, whereas NAPA has a half-life of six to nine hours in patients with normal creatinine clearance. Thus NAPA, the active metabolite, will accumulate within the system and at its site of action.[16]

A patient's clinical status can also dramatically alter drug utilization patterns. Hepatitis impairs the metabolism of drugs. If the liver has lost its reserve capacity, patients with hepatitis can become severely intoxicated when given drugs dependent upon hepatic degradation. Congestive heart failure can significantly alter the distribution of drugs to tissues, thus precipitating altered drug utilization and response patterns.

Renal excretion: Urinary excretion eliminates most drugs and their metabolites. Changes in renal function will alter plasma concentrations of any drug not extensively metabolized. Impaired renal function may elevate drug plasma concentrations.

Renal drug clearance is decreased in uremic patients and in those with congestive heart failure. Interestingly, drug metabolites are so water-soluble that a significant decrease in urinary output will not, of itself, result in increased plasma concentrations of most conjugated drug metabolites.[1–16]

Table 3. Information needed for interpreting drug levels

Patient's age, weight, and sex
Names and dosages of all drugs the patient is receiving
Total daily dose of all drugs
Dosage regimen and form of each drug
Time the last dose was administered
Clinical status of the patient
Time the specimen was drawn

Pharmacogenetic alterations of drug disposition in healthy individuals: Genetic factors significantly affect drug clearance. If a large patient population were given the same mg/kg dosage of a drug, individuals within the population would differ markedly in their ability to utilize the drug. Genetic differences are reflected in the marked variability of the steady-state plasma concentrations observed.[1–5,17,18]

For example, in a patient population receiving phenytoin at a standard therapeutic dose of 5 mg/kg/day, one would theoretically expect all patients to have a therapeutic drug level of 15 μg/mL. In reality, plasma concentrations will range from 0 μg/mL, which suggests drug malabsorption, noncompliance, or fast drug metabolism, to levels of 40–50 μg/mL, which may indicate drug reactions, hepatic or renal disease, or genetically slow drug metabolism.[9]

Consider the incidence of fast and slow metabolism in patients receiving isoniazid, which is commonly used to treat tuberculosis. Approximately 40% of all Caucausians are rapid acetylators of isoniazid, whereas in Japanese and Eskimos, the rate is 90%. Such genetic variability requires individualization of therapeutic regimens to ensure optimal isoniazid concentrations.

Interpretation of drug concentrations

Individuals vary widely in their utilization of drugs as a direct consequence of genetic factors, multiple drug therapy, age, and weight. Successful TDM individualizes drug therapy based upon assessment of plasma concentration, the patient's clinical status, and the therapeutic goals. To maximize knowledge of the patient's pharmacological status, each laboratory engaged in TDM should have the following information available when a drug is monitored.[1–18] (*Table 3*):

Age: There are marked age-dependent differences in drug utilization, particularly in the transition between neonate and infant, child and adolescent, and adult and the elderly.

Weight: The patient's weight is essential for mathematical calculations of the relationships between the drug dose, plasma concentration, and drug clearance. Any factor altering drug half-life (clearance) will alter the drug's steady-state concentration. During multiple drug therapy, two drugs may compete for the same metabolic site. This competition will decrease the metabolic rate of the drug excluded from the site and prolong its half-life. Since the half-life is prolonged (clearance is decreased), a new, higher steady-state drug concentration will be achieved and maintained, as long as multiple drug therapy is continued.

Other drugs: Knowledge of other drugs being taken is essential for identification of potential drug interactions which might alter plasma concentrations as well as for the identification of compounds which may interfere with a given analytical technique. Multiple drug therapy can also alter absorption, protein-binding, and renal clearance of a given agent. Change in any of these factors can result in altered steady-state concentrations.

Total daily dosage: Knowledge of the total daily dosage for each drug administered is necessary to mathematically determine the patient's total daily drug dose in mg/kg. Without this information it is impossible to correlate the patient's actual with his expected plasma concentration. Knowledge of the mg/kg dose allows the prediction of the patient's expected plasma drug concentration using the concentration:dose ratio (CDR) for that drug. Predicted drug concentrations can then be correlated with the observed (measured) drug concentration.

Clinical status: Acute or chronic disease can dramatically alter drug utilization patterns, especially in hepatitis or renal failure. Drug clearance is dramatically altered by renal and liver disease because the rates of drug elimination are changed. New steady-state levels may differ significantly from those observed in healthy individuals. Without knowing the clinical status of the patient, it is impossible to distinguish an altered drug utilization pattern associated with a given disease state from other factors (non-compliance, drug interactions, etc.) which can present with a similar pattern.

Critical time intervals: Knowing when the last drug dose was administered and when the last specimen was drawn is essential for assessing whether the actual plasma concentration represents a peak or trough. Knowledge of the actual sampling time and dosage interval is vital for accurately interpreting plasma concentrations of drugs with short half-lives, such as theophylline and lidocaine.

As a rule, specimens for TDM should be drawn at a trough, i.e., when the concentration is lowest for that dose interval. Measurement of peak concentrations after oral administration is difficult because of marked inter-individual variability in drug absorption patterns. Peak levels are indicated, however, in certain situations after IV administration, and are reportedly useful in monitoring antibiotics, theophylline, valproic acid, and certain antiarrhythmic drugs.

When a specimen is drawn in relation to drug administration depends on the pharmacokinetic properties of the drug and the dosage form. The patient should be at or near steady state. After dose adjustment, equilibrium should be reestablished with the new dosage regimen before another specimen is drawn. Specimens drawn immediately before administration of the next oral dose provide trough serum levels for drugs administered on a continuous basis; the trough level ideally should be above the minimum effective serum level. Specimens for peak levels are generally drawn 15–30 minutes after IV administration, one to two hours after intramuscular (IM) administration, and one to five hours after oral administration (depending on the rate of drug distribution). When the specimen is to be drawn during an infusion, it should be taken from the opposite limb.

Plasma drug concentrations must always be interpreted in conjunction with the clinical status. The clinician should be concerned with optimal concentrations, not therapeutic ranges. The optimal concentration of a drug is defined as that present in plasma or some other biological fluid or tissue which provides the desired therapeutic response in most patients. The severity of the disease process determines the amount of drug necessary to achieve a given therapeutic effect. Thus it is possible that the desired therapeutic effect may be achieved at a plasma concentration well below the optimal range. Other patients may require levels above those usually deemed optimal, and may tolerate these levels without evident

toxicity. Still others will not achieve the desired therapeutic effect even with plasma concentrations in the toxic range. If the desired therapeutic effect is achieved at suboptimal plasma concentrations, the dose should not be increased. The dose should be increased in a second patient who does not achieve the desired effect at a suboptimal plasma level, and prescribing additional drugs simply to increase the plasma concentration into the therapeutic range should be avoided. Obviously, the interpretation of plasma drug concentrations must incorporate factors which can alter the steady-state plasma concentration achieved on a given dosage regimen.

Determining dosage intervals: Generally, in order to maintain a constant steady-state drug concentration, dosage intervals should be half of each drug's half-life. For example, phenytoin is given every 12 hours since its half-life is 24 hours. Primidone would be given every three hours, since its half-life is six to eight hours with polytherapy; in monotherapy it would be every eight hours since its half-life is 15 hours.[9]

Short dosage intervals (three to four hours) are often impractical in our patients, but drugs with short half-lives should be administered at least once each half-life. The goal is to maintain the trough drug concentration above the minimum effective concentration (MEC), while avoiding peak concentrations which reach toxic levels. An appropriate steady-state concentration will be maintained so long as the dosage schedule and the interval between doses allow no significant fluctuations between peak and trough concentrations. If the dosage interval exceeds the half-life of the drug, plasma concentration just prior to the next dose may not provide the desired therapeutic effect. For example, a patient whose phenytoin level falls from 14 μg/mL to 9 μg/mL may have a seizure at the lower level but not at the higher. Adhering to an appropriate dosage schedule allows plasma concentration to remain within the optimal therapeutic range at all times.

If a patient's drug absorption is very rapid, or if dosage intervals are excessively short, he may experience drug intoxication which presents clinically with symptoms characteristic of that drug. These symptoms appear transiently at fixed intervals after drug administration. Toxicity results from a peak plasma concentration above the optimal range shortly after drug administration. Side effects may be eliminated by increasing the dosage interval or decreasing the dose.

Monitoring steady-state drug concentrations: When long-term oral therapy is initiated, the drug will accumulate within the body until the rate of clearance (elimination) equilibrates with the total daily intake. The time required to reach a stabilized steady state is seven half-lives after institution of drug therapy or alteration of total daily dose, although steady-state processes are 97% complete within five half-lives. If one knows when the drug therapy was initiated, one may extrapolate steady-state plasma concentrations by correcting for the number of half-lives expired before sampling. This technique, however, provides only a rough estimate of the expected steady-state concentrations. The pharmacological activity of the drug may be eliminated even though its metabolite is still present, and a sudden change in measured steady-state drug concentrations usually indicates altered disposition of the pharmacologically active (parent) compound.

Conclusion

The clinical utility of TDM in managing patients is firmly established. The number of drugs routinely monitored will continue to grow, and the success of this expansion will depend on the development and application of current technologies as well as on the growth of new ones. Over the next few years, because of their reliablity and ease of operation, the major technologies for drug monitoring will likely be the homogeneous enzyme immunoassay system and HPLC. Continuing education of both physicians and laboratory personnel in the new technologies and their clinical application is essential to ensure appropriate application of TDM in improving patient welfare.

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