Paparella: Volume I: Basic Sciences and Related Disciplines

Section 6: Pharmacology:

Chapter 27: Principles of Pharmacology

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Drugs have been administered to treat ailments and suffering for centuries. These treatments give both subtle and dramatic therapeutic benefits that can usually be seen by the watchful eye of the clinician. Medicine has devoted enormous amounts of time, energy, and resources to improving tools and techniques for disease diagnosis. Modern technology has stimulated similarly dramatic advances that are aimed at improving drug therapy benefits and reducing adverse effects. The central discovery has been the ability to measure drug and drug metabolite concentration (therapeutic drug monitoring) and to describe the behavior of these concentrations in patients (pharmacokinetics). In this chapter, we describe how to gain a therapeutic advantage by applying the basic principles of pharmacotherapy.

Balancing Drug Efficacy and Toxicity

The ability to control the efficacy and toxicity of prescribed drugs is the key to achieving the best therapeutic outcome. The parameters for monitoring drug therapy are the desired therapeutic responses and the undesired toxic responses. For example, therapeutic response is easily monitored in hypertension, since blood pressure reduction is easily measured. In other disease states, however, therapeutic end-points are much more difficult to observe over a short period of time. This is particularly true when the disorder is not of continuous intensity. In epilepsy, for example, rapid assessment of the therapeutic effect of a drug and its dose is difficult because of the intrinsic variability of seizure activity.

An important premise of pharmacotherapy is that the response to a drug is related to the concentration at the target organ receptor site. Since this concentration can seldom be measured, therapeutic drug monitoring is based on the concentration in the blood, which is one step removed from the desired measurement. The relationship between the concentration in the blood (serum or plasma) and the pharmacologic effect has been established for many drugs, and measurement of this concentration should become part of the treatment plan when any of these agents are used. Several of these drugs and their therapeutic ranges are shown.

Dosage guidelines published in the package insert and *Physician's Desk Reference* have been established for all legend drugs. Most dosage guidelines were developed during the early clinical trials and have undergone little examination since that time. This is true for old drugs, such as digoxin, as well as for newer ones, such as bretylium. Typically, normal doses were determined in comparatively young patients without multiple diseases, and this population may not be representative of the population who is treated with the drug.

Factors Influencing Drug Dosage

It is generally understood that drugs affect each patient differently. It is also true that patients affect the action of drugs differently. Patients with diseases that affect the liver or kidneys, which are the major organs of drug elimination, will have decreased elimination and higher frequency of toxicity when given drugs in their conventional doses

Renal Disease. For patients with renal failure or reduced function, the extent of dose modification necessary depends on two factors: the degree of renal impairment and the amount of the drug or active metabolite normally excreted in the urine. If the kidney is a major route of elimination for a drug, even a small degree of renal impairment can have a substantial effect on drug concentrations and predispose the patient to toxicity. A patient with no other clinically important signs of renal impairment can have significant changes in drug excretion, and, therefore, require drug dosage modification. Age-related decreases of renal function must be taken into consideration. Elderly patients have reductions in glomerular filtration rate, number of functioning nephrons, and active tubular secretion.

Liver Disease. Similarly, hepatic dysfunction can lead to an abnormal accumulation of drugs that require liver metabolism for elimination. Unfortunately, it is more difficult to predict changes in drug metabolism in patients who are elderly or who have hepatic disease than in those with renal disease. Attempts to correlate results of liver function tests with drug elimination have not been successful, making measurement of serum concentrations in such patients essential.

Heart Failure. Although the relationship is less obvious than with renal or hepatic disease where the organ of drug elimination is directly involved, congestive heart failure may also cause dramatic changes in drug absorption, distribution of the drug in the body and, elimination of the drug. With a reduction in cardiac output, mesenteric blood flow is reduced, sometimes to the extent that a portion of bowel becomes ischemic. Therefore, absorption of orally administered drugs may be reduced, the effect being most pronounced for drugs with slow absorption such as sustained-release products. Blood flow to the liver and kidneys can also be reduced, slowing drug elimination. Finally, blood flow to tissues, like skeletal muscle that serve as binding sites for drugs, can be markedly reduced. When tissue binding is incomplete, the serum concentration can remain high. These changes in drug concentration can occur in patients with only mild reductions in cardiac output.

Protein Binding. A number of diseases can affect binding of drugs to plasma proteins. Only the unbound or free circulating fraction of a drug is able to cross cellular membranes and elicit pharmacologic responses, both therapeutic and toxic. Previously, drugs were thought to be bound primarily to one plasma protein, albumin. Phenytoin (Dilantin), valproic acid (Depakene), salicylates, and warfarin sodium (Coumadin, Panwarfin) are examples of drugs that bind to albumin. Recently, many drugs have been discovered to be highly bound to another plasma protein, alpha-1-acid-glycoprotein. Lidocaine (Xylocaine), quinidine, propranolol (Inderal), phenothiazines, tricyclic antidepressants, narcotic analgesics, and many cancer chemotherapeutic agents are examples of drugs in this group.

Drug binding to albumin is affected by hepatic disease, age, interactions with other drugs, and chronic renal failure. Patients who are elderly or whose liver function is impaired have decreased amounts of albumin available for drug binding. If a patient is given two drugs that bind to albumin, one drug may displace the other from binding sites. Uremic patients also have altered drug binding to albumin.

Alpha-1-acid-glycoprotein, an acute-phase reactive protein, is released in high concentrations during times of stress of inflammation. Increased concentrations have been documented after surgery and myocardial infarction and in patients with cancer or an inflammatory disorder. This changes the amount of free drug available to exert both desired therapeutic actions and toxic effects.

Absorption. The distinction between absorption and bioavailability is important in pharmacotherapy. Absorption of an oral drug refers to the fraction of a dose that is dissolved and subsequently absorbed from the lumen of the intestine. Bioavailability refers to the fraction of the dose that actually reaches the systemic circulation. An oral drug reaches the hepatic portal venous system after absorption and is delivered to the liver in high concentrations before tissue distribution. Its bioavailability is the fraction of the dose remaining after losses from incomplete absorption and from metabolism when the drug takes its "first pass" through the liver. Some oral drugs have good absorption but low bioavailability. Bioavailability is the more important parameter for predicting pharmacotherapeutic effects.

Gastrointestinal diseases may reduce absorption of oral drugs, as may radiation of the abdomen. Drug absorption is frequently reduced in the elderly because of age-related decreases in intestinal motility and the number of mucosal cells. In addition, the overall decrease in metabolic activity in this age group has a negative effect on absorption.

Verapamil (Calan, Isoptin), a calcium-entry antagonist, is available in intravenous and oral forms for treatment of angina pectoris and supraventricular tachydysrrhythmias. According to the manufacturer's literature, oral verapamil has complete absorption. However, its bioavailability is low because of a high percentage of inactivation by first-pass hepatic metabolism. Therefore, to achieve the same effect, oral doses of verapamil must be larger than intravenous doses.

Metabolism. Other conditions that change a drug's metabolism can alter the extent of its pharmacologic effect. The detrimental effects of smoking on a patient with pulmonary disease are clear, but also important are the changes induced by smoking on theophylline therapy. Smokers often require larger doses of theophylline than nonsmokers because of an increased rate of theophylline metabolism.

Ethanol intake affects not only the patient's health but also the patient's response to such drugs as diazepam (Valium), phenytoin, and warfarin sodium. Ethanol interactions with diazepam and warfarin sodium are complex, altering both metabolism and pharmacologic activity and resulting in either an enhanced or a diminished response.

Distribution. Several factors that can influence an elderly patient's response to drugs have already been mentioned: reduced renal excretion, hepatic metabolism, absorption, and protein binding. In addition, older patients typically have different body composition than younger patients. Older patients usually have less water content and less lean tissue and more fatty tissue. This can affect the patient's response to drugs that preferentially distribute to water (eg gentamicin), lean tissue (eg digoxin), or fat (eg phenobarbital). Also, women typically have more adipose tissue than men.

Children. Just as dosage requirement for adults change as they move into old age, dosage requirements for children change as they grow into adulthood. Unfortunately, pediatric dosage requirements are only now being critically studied. Neonates have reduced renal and hepatic function, whereas children have faster renal and hepatic elimination than adults. Water content and fat content of the body also change as children grow.

At the beginning of puberty, elimination of drugs such as anticonvulsants and theophylline rapidly slows to the adult level. Drug toxicity is a special hazard at this time because the reduction in drug elimination occurs before most of the other characteristics of puberty become apparent. Therefore, therapeutic drug monitoring in children is particularly important during the years when puberty is most probable.

Considerations When Measuring Drug Concentrations

Drug distribution and elimination, and body mass vary greatly from individual to individual; therefore, the same dose does not achieve similar concentrations in all patients. For a serum concentration of a drug to be clinically useful, the relationships between the concentration and pharmacologic effects must be known. When efficacy is being assessed, there must be an established relationship between concentration and therapeutic effect. When toxicity is being assessed, there must be an established relationship between concentration and toxicity. These relationships are most often established on the basis of population frequencies.

Effect-Concentration Relationship. As serum concentration increases, more patients exhibit the desired pharmacologic effect. The incidence of adverse effects also increases as the drug concentration increases. The relationship between concentration and incidence of toxicity varies for different toxic effects. In addition, there may be a low incidence of hypersensitivity reactions that are independent of drug concentration.

For most drugs in clinical use, the desired effect is obtained in a high percentage of patients at concentrations that cause few serious toxic effects. The therapeutic range of concentrations is the range in which the therapeutic effect is observed in a high percentage of patients and serious toxic effects are observed in a low percentage of patients. For many drugs, only about 80 per cent of patients achieve the desired effect with single-drug therapy. It is important to remember, however, that the therapeutic range is based on population data. A particular patient may achieve the desired effect at a low concentration or may require a concentration higher than the population's therapeutic range to achieve the desired effect.

Similarly, a particular patient may experience adverse effects at a concentration well below the therapeutic range.

The therapeutic range is useful as an initial goal of therapy and as a parameter for monitoring drug therapy when the pharmacologic effects are not easy to identify. When the relationship between drug concentration and effect in an individual patient is known, that information is more useful than the population-based therapeutic range. For example, an asthmatic adult continued to have symptoms with an oral theophylline regimen that produced a serum concentration of 18 micrg/mL but experienced relief of symptoms when the regimen was changed to produce a concentration of 23 microg/mL. If there are no symptoms of toxicity, there is no reason to reduce the dose, even though the usual therapeutic range of theophylline concentration is often thought to be 10 to 20 microg/mL. In the future, this patient's theophylline regimen should continue to be tailored to produce serum concentrations greater than 18 microg/mL.

Measuring Drug Concentrations. Drug serum concentrations should be measured when the difference between therapeutic and toxic concentrations (therapeutic index) is narrow. Penicillin has a wide range of safety in nonallergic individuals. Penicillin can usually be given in dosages that achieve several times the minimum inhibitory concentration without producing toxicity, and therefore, its serum concentration rarely needs to be measured. In patients with poor renal function, extremely high concentrations may develop, resulting in penicillin-induced seizures. However, drug monitoring is crucial for drugs that can cause serious toxic effects at concentrations only slightly above the therapeutic range.

Serum concentrations should also be measured when the dosage form of a drug is changed. When a patient whose condition has been stabilized with an intravenous drug is switched to a long-term oral regiment of the same drug, the concentration should be measured to ensure that an adequate amount of the oral drug is being absorbed. If the preparation of an oral drug is changed, serum drug concentrations should be measured to ensure equality. A switch from oral quinidine sulfate to oral quinidine gluconate (Duraquin, Quinaglute Dura-Tabs) may reduce the therapeutic effect because of the change in percentage of quinidine in the medication and a change in extent of absorption. A switch from conventional oral procainamide to one of the sustained-release procainamide products may have a similar effect on therapeutic response because of a decrease in absorption. Table summarizes the clinical situations, patient characteristics, and drug characteristics that suggest when drug concentration monitoring would be most beneficial.

Loading Dose. When rapid pharmacologic control of a disorder is desired, a loading dose is often administered to quickly achieve a therapeutic serum concentration. A loading dose is larger than the normal maintenance dose. The amount of drug required for a loading dose depends on the desired serum concentration, which, in turn, depends on the need for an immediate result and the size of the patient. A large patient needs a larger loading dose than a smaller patient, and lean or ideal body weight is often a more reliable parameter than actual weight for drugs that do not enter adipose tissue.

Maintenance Dose. Once therapeutic concentrations are achieved with a loading dose, the effect is maintained with maintenance doses. For almost all drugs, each subsequent dose is administered before all the drug from previous doses is eliminated. Therefore, a drug accumulates in the body, and with continued dosing, a drug will continue to accumulate until an equilibrium (steady state) is reached between the rate of drug administration and the rate of drug elimination.

Steady State. The serum concentration of a drug when this equilibrium is reached is the steady-state concentration. The time required to reach steady state depends only on the drug's elimination half-life. After one half-life, the concentration is 50 per cent of the steady-state concentration. After four to five half-lives, steady state is essentially reached. Therefore, a rough estimate of a drug's half-life is necessary to known when the steady state will be reached.

Considering when the drug concentrations reach steady state is important for two reasons. The patient's clinical response to a given dose is best assessed after the steady state has been reached, and serum concentration should be measured at the steady state to best reflect chronic efficacy or toxicity. If the patient's clinical response or serum concentration is measured too soon after starting a drug and the dose is increased in response to low concentrations, toxicity may be observed when the steady state is eventually reached. After any adjustment in dose, five half-lives must again elapse before the new steady state is reached. Also, if the clinical assessment is made too soon, a drug may be prematurely judged to be ineffective and, therefore, discontinued or used in combination with additional agents. It is important to understand that steady-state concentrations are not necessarily the same as therapeutic concentrations.

The goal is to achieve similar therapeutic concentrations with both the loading dose and the maintenance regimen, but the serum concentrations achieved after the loading dose and after the steady state is reached are not always identical. The loading dose may achieve the desired concentration, higher (potentially toxic) concentrations, or lower (potentially subtherapeutic) concentrations. Similarly, the steady-state concentration may be toxic, therapeutic, or subtherapeutic, depending on whether the selected maintenance dose is too large, ideal, or too small, respectively. Therefore, approximately five half-lives must pass to allow observation of the ultimate effect of the maintenance dose, even if an ideal loading dose achieved a therapeutic concentration or response.

Measuring serum drug concentrations can also be used to minimize the drug dose. This would reduce the patient's exposure to potential toxicity and reduce the overall cost. An example is vancomycin, with which experience has shown that the majority of adults achieve effective concentrations when given doses once or twice daily as opposed to the recommended four times daily.

Pharmacokinetics. The study of pharmacokinetics is an attempt to mathematically describe the behavior of a drug in the body. Some common pharmacokinetic terms are listed.

Chronopharmacokinetics. Recently, it has been shown that the variation in drug effects is a function of circadian and other biologic rhythms. Several drugs have been demonstrated to

exert very different quantitative pharmacologic effects when given at various times of the day or night. These differences have been incorporated into time-specific dosage regimens to reduce toxicity of some cancer chemotherapy regimens involving Adriamycin and cis-platinum. Time-dependent alterations in drug elimination have been shown for several commonly used drugs including theophylline, cyclosporine, aspirin, and propranolol.

Drug Concentrations and Effects

The relationship between drug serum concentrations and pharmacologic effect (pharmacodynamics) is known only when the serum concentration is in equilibrium with the tissue concentration. After an intravenous drug dose is given, the drug remains in high concentration in the blood for a short time until it can equilibrate into the tissues. In most cases, the high serum concentrations measured before tissue penetration has occurred are not related to clinical effect. A serum concentration measured too soon after an oral dose may not accurately reflect the concentration after complete drug absorption, a fact that is even more pronounced with sustained-release products.

Measurement of trough concentrations, which are usually reached just before administration of the next dose, is a convenient way to avoid this problem. When the drug is given orally, there is the additional problem of the time required for absorption. Again, in most cases, measurement of trough concentrations is recommended to avoid this problem in long-term oral therapy.

If the previous dose was administered earlier or later than usual, the trough concentration measurement may not reflect the normal steady-state trough concentration. This problem often occurs with three- and four-times daily dosage regimens (TID, QID) when fewer doses are taken during the night. Therefore, it is important to know and record the time the blood is sampled and the actual time the previous dose was administered.

Patients can often be treated effectively with fewer drugs if the dosage of each is optimized. Since the application of therapeutic drug monitoring, epilepsy is well controlled by a single drug in many more patients than before. Compliance tends to be better when fewer drugs are prescribed and dosage is less frequent. Also, the fewer drugs used, the less probability of serious adverse drug reactions or interactions.

Toxicity. In addition to measurement of trough concentrations at the steady state, the serum concentration of a drug should be measured whenever toxicity is suspected. A high serum concentration with symptoms of possible toxicity helps to validate the suspicion of a drug effect. In this situation, measurements can be made without regard for the steady-state condition or the time of dose administration.

Compliance. Serum concentration determinations are also helpful to assess patient compliance with a drug regimen. However, poor compliance is not the only cause of low concentrations; rapid elimination or poor absorption could also be responsible. Low

concentrations are often found in patients receiving long-term drug therapy. If the patient's disorder appears to be well controlled with a "subtherapeutic" serum concentration, two possibilities must be considered. The patient may respond at concentration lower than the population-based therapeutic range or the patient may not require long-term drug therapy.

Drug Interaction. Another situation in which measurement of drug concentration is often helpful is that in which two or more drugs with the potential for drug-drug interactions are being administered simultaneously. Some drug interactions result directly from the pharmacologic effect of each drug. However, many drug interactions are due to changes in the absorption, binding, or elimination of one drug that is altered by the other. By measurement of drug concentrations and consideration of possible mechanisms of interaction, drug interactions can often be anticipated and prevented before toxicity or loss of therapeutic effect occurs. Also, some drug interactions are beneficial, such as the combination of trimethoprim and sulfamethoxazole (Bactrim, Septra).

Efficacy. In most clinical situations, a single measurement of the drug serum concentrations at the steady state is adequate to help assess the effectiveness of drug therapy. The relationship is constant between dose and the steady-state concentration in an individual patient for almost all drugs in the clinical range of doses. Therefore, to achieve a 50 per cent increase in concentration, the dose is increased by 50 per cent. This simple technique cannot be applied to several commonly used drugs, including phenytoin and ethanol, since their elimination processes are saturable and can lead to rapidly increasing drug concentrations after small increases in dose.

In some situations, the correct dose is more rapidly determined by serial measurements of drug serum concentrations to calculate the extent of drug distribution and elimination. This factor is true when the severely ill patient is treated with drugs that vary greatly in body distribution and elimination. A patient with a gram-negative infection who is being treated with tobramycin is a common example. Sometimes, intensive monitoring is also helpful in determining the mechanism of unexpected results, such as alteration in absorption, distribution, or elimination. An abnormality in one of these processes may be the cause of therapeutic failure or toxicity.

Despite anticipated changes in a drug response, measurement of serum concentrations of all drugs in all patients may not be indicated if some other measure of a drug's effect can be used. However, there are a number of situations in which measurement of drug concentrations can be extremely helpful. One prime example is that of the severely ill patient who needs rapid, effective treatment, for example, a patient with gram-negative pneumonia, in whom a sufficient concentration of antibiotic must be achieved early in therapy. In this situation, the main advantage of drug monitoring is that it minimizes the time required to find the proper dose. A different advantage can be obtained in the stable chronically ill patient. If such a patient is going to receive a drug for a long period, perhaps for life, drug monitoring can ensure that the best possible dosage regimen is being provided.

Drug concentrations should be measured when agents are added to the regimen and also when they are discontinued. As the number of prescriptions for cimetidine (Tagamet) has

increased, so has the number of reports of toxicity and the interaction of reduced elimination of other agents when this drug is added to the patient's regimen. For example, theophylline concentration should be measured to prevent toxicity when cimetidine is added and again to prevent loss of therapeutic control when cimetidine is discontinued.

Therapeutic drug monitoring facilitates the quantification of each patient's pharmacologic response. It is important to note that a pharmacologic solution may generate its own problems; therefore, therapeutic drug monitoring is a dynamic process rather than an isolated instance. This process has two major components: the generation of evidence that a drug is (1) producing a desired effect and (2) not producing unwanted effects. Only when both are accomplished will each drug's therapeutic benefits be exploited to the fullest.