Applied Clinical Pharmacokinetics

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Preface

The major objective of *Applied Clinical Pharmacokinetics* is to offer students and clinicians in pharmacy, medicine, pharmacology, and clinical chemistry a practical guide to clinical pharmacokinetics. Introductory chapters provide the reader with a background in basic pharmacokinetic principles. These concepts are reinforced in the chapters covering specific therapeutic agents. Each chapter covers important aspects of clinical pharmacology, pharmacokinetics, plasma concentration and response relationships, dosage regimen design, and assay methods. Practice problems and their solutions are included in each chapter to assist the reader in applying the information presented.

A section on programmable calculators includes numerous, practical programs that will facilitate the understanding and application of complex pharmacokinetic relationships. These programs provide a user-oriented format that prompts the individual to supply necessary information for solving pharmacokinetic problems. Areas covered by these programs include one- and two-compartment equations for all routes of administration, estimation of the area under the curve, a curve stripping routine, aminoglycoside, theophylline, and phenytoin dosing, salicylate and warfarin kinetics, and population kinetics estimates.

This text will provide the student with a logical and complete appreciation of the clinical pharmacokinetics of a wide range of therapeutic entities and enable the clinician to apply this knowledge to future patient care situations.

Dennis R. Mungall, Pharm. D.

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Pharmacokinetics: An Introduction

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The use of pharmacokinetic principles to individualize drug therapy in clinical practice has evolved as a result of advances in clinical pharmacology, analytical chemistry, and biopharmaceutics. Pharmacokinetic and pharmacologic studies have demonstrated large interpatient differences in the absorption, distribution, and elimination of numerous drugs with a narrow therapeutic index (1–6,12). These, in addition to others, include the aminoglycoside antibiotics, quinidine, procainamide, theophylline, phenytoin, salicylates, lidocaine, and the digitalis glycosides. Each of these demonstrates a correlation between serum concentrations, the therapeutic response, and toxicity. The purpose of this chapter is to present relevant concepts of pharmacokinetics and the applications of these concepts to clinical practice.

DEFINITION

Pharmacokinetics is concerned with the study of the time course of drug absorption, distribution, metabolism, and excretion and with the relationship of these variables to the intensity and time course of therapeutic and adverse effects of drugs (19). *Biopharmaceutics* is a pharmaceutical science encompassing the study of the relationship between the nature and intensity of biologic effects and the various formulation factors such as the chemical nature of the drug, inert formulation factors, and the pharmaceutical processes used to manufacture the dosage form (19). The nature and intensity of biologic effects are generally proportional to the total amount of drug made available to the body. The rate of drug delivery is judged by the efficiency with which it can make the drug available to the body. If two formulations produced identical serum concentrations, they would be considered *bioequivalent. Bioavailability* is a measure of the extent of drug absorption from a dosage form (19) and differences in bioavailability can be the result of formulation differences or physiologic and pathologic states of patients.

SYSTEMIC AVAILABILITY

When a drug is administered orally or intramuscularly, it must be released from its dosage form before the absorption process begins. Figure 1 illustrates the steps in the absorption phase. The rate limiting step for absorption is dissolution. This is governed

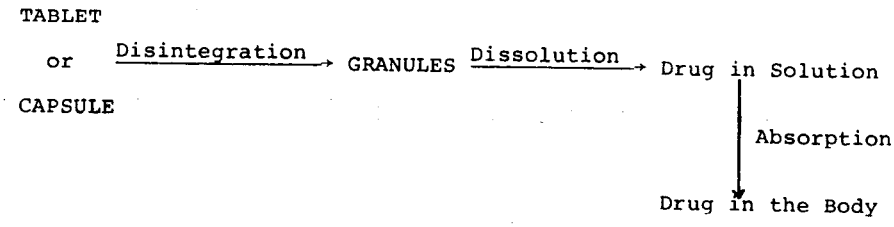

FIG. 1. Drug absorption.

by several physiochemical properties of the drug, such as the aqueous solubility of the drug, acid-base characteristics, the crystal form, and particle size. The major site of absorption is the small intestine. Physiologic factors affecting bioavailability include gastric emptying time and intestinal motility. After absorption occurs, drug molecules pass through the liver and enter general circulation for distribution in the body. Biotransformation by the liver can occur at this point and this is called the "first pass effect" (Fig. 2). Examples of oral drugs that are subject to the first pass effect are isoproterenol, terbutaline, propranolol, imipramine, and the nitrates. The parenteral dose of such drugs is, therefore, considerably smaller than the oral dose.

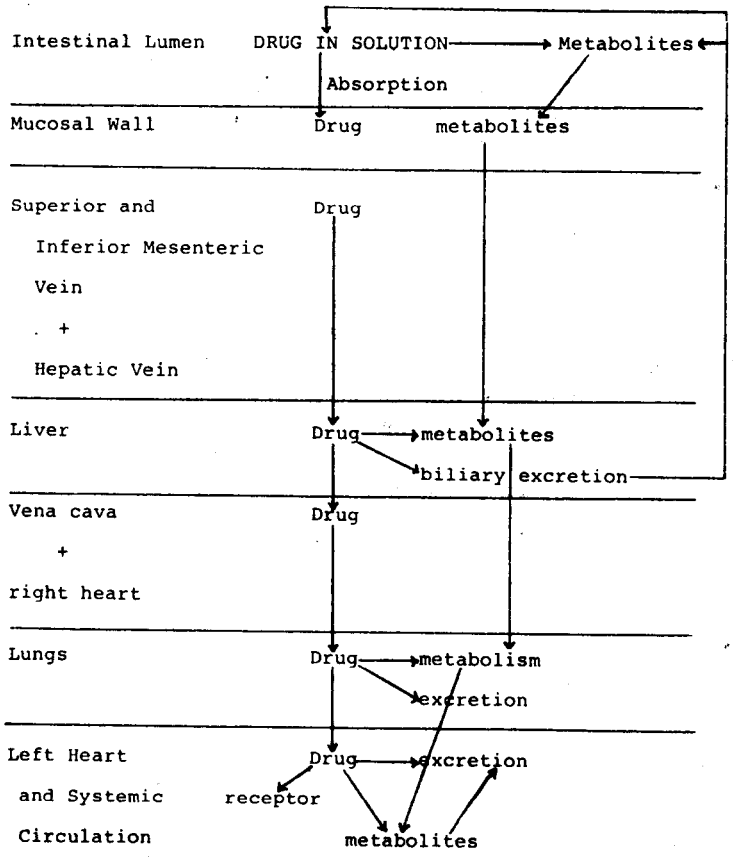

FIG. 2. The first pass effect.

TABLE 1. *Factors influencing gastrointestinal absorption*

Group	Factor	Effect
Gastric emptying	Volume of meal	Increasing volume of ingested material results in initially increased gastric emptying, followed by decrease in emptying rate. Liquids are more rapidly emptied than solid material.
	Type of meal	Fats decrease emptying rate.
	Viscosity	Increasing viscosity reduces rate of emptying.
	Osmotic pressure	Increasing osmotic pressure reduces rate of emptying.
Intestinal motility Transit time	Food viscosity	Solid food delays transit time. Increased viscosity delays transit time but decreases rate of dissolution and diffusion, too.
Splanchnic blood flow	Food	Food uptake increases blood flow in splanchnic area.
	Physical work	Hard physical work decreases blood flow in splanchnic area.

Table 1 lists several other variables that affect gastrointestinal absorption of drug. Food taken with drugs is an important practical consideration and various types of meals affect intestinal transit differently. The presence of food affects the pH of intestinal contents and alters the unionized:ionized drug ratio. The complex influence of food on drug absorption prevents any general statements.

Drug interactions may also affect absorption of drugs (Table 2). A classic example is tetracycline and calcium forming an insoluble complex and preventing absorption of the tetracycline. Drugs may also affect gastric emptying and intestinal motility, pH of luminal contents, perfusion of GI tract or metabolic organs, or in some other way prevent or enhance absorption.

TABLE 2. *Drug interactions affecting gastrointestinal absorption of drugs*

Changes in gastric or intestinal pH	Antacids
Changes in gastrointestinal motility	Cathartics Anticholinergics
Changes in gastrointestinal perfusion	Cardiotonics Vasodilators Pressors Antiarrhythmics
Interference with mucosal function	Neomycin Colchicine
Chelation	Tetracycline and calcium, magnesium, aluminum, or iron
Exchange resin binding	Cholestyramine and acidic drugs
Absorption	Charcoal, kaolin antacids
Solution in poorly absorbable liquid	Mineral oil

DRUG DISTRIBUTION

It is useful to consider the case of a drug administered in a single dose, either intravenously or orally, to define the meaning and significance of several important pharmacokinetic terms. Following intravenous injection, the drug becomes mixed in the plasma; it may become partially bound to plasma proteins and adsorbed to erythrocytes and diffuses to various degrees into red blood cells and to extravascular tissues. These processes of distribution usually cause a rapid initial decrease of drug concentration in the plasma. The subsequent decline of these concentrations is due to the elimination of the drug from the body by processes such as biotransformation by tissues, renal excretion, and biliary excretion. The decline of drug concentration in the plasma is accompanied by a parallel decline of drug concentration in those organs and tissues that contain a significant fraction of the total amount of drug in the body (Fig. 3).

Distribution and elimination are very often described by the use of models. The most frequently used models are the one- and two-compartment open models with elimination from the central compartment. The one-compartment model assumes that the distribution process is instantaneous, whereas the two-compartment model assumes that there is a significant distribution phase.

Volume of distribution (Vd) is a term often used to describe the extent of distribution of a drug. It does not tell us where the drug is in the body and is not a real number reflecting any physiological compartment. Vd is an abstract number that is useful in determining the size of the dose required to reach the desired blood concentration of a drug.

Important factors that can affect the site and extent of distribution include blood flow to tissues, lipid solubility, regional differences in pH, and the degree of protein binding.

In diseases such as congestive heart failure, cardiac output and perfusion of blood to the tissues are impaired. Impairment of perfusion to the tissues can lead to a decrease in the volume of distribution. A reduction in the Vd can lead to an increase in serum drug concentrations and for drugs with narrow therapeutic indices, such as lidocaine, this can lead to an increased risk of toxicity.

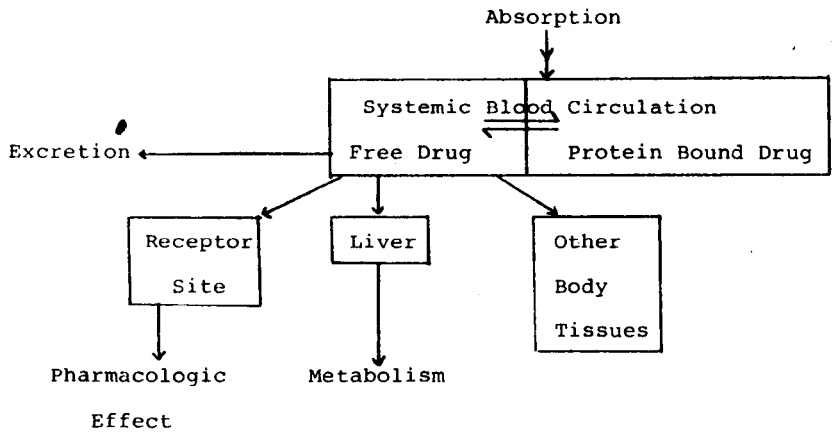

FIG. 3. Drug distribution.

Lipid solubility of the drug is important in determining if a drug will be significantly distributed to adipose tissue. This becomes important when determining maintenance dosages of drug for overweight patients. If total body weight is used to estimate dosage requirements and the drug does not distribute to adipose tissue, an overestimate in the dose can be made. Drugs such as digoxin have been shown to be minimally lipid soluble and thus dosage requirements are based on ideal body weight.

Regional differences in pH can lead to localization of drugs in various tissues. Two important examples of this phenomenon involve excretion of drugs in breast milk and urine. Breast tissue has an acidic pH and this leads to trapping of alkaline drugs such as caffeine. The mechanism of this is that the unionized alkaline drugs are able to pass into this environment and then ionize secondary to the acidic environment. It has been shown that only the unionized moiety is able to pass through the lipid cellular membranes. A second example of trapping is that of urinary excretion of certain drugs. In the case of salicylic acid, a substantial increase in excretion will occur if the urine is alkalinized. This leads to an increase in the percentage of ionized drug in the urine that cannot pass through the lipid membrane of the nephron.

A final determinant of the extent of distribution is protein binding. When drugs enter systemic circulation, they are bound to varying degrees by plasma proteins, mainly albumin. The portion of drug bound to plasma proteins is unable to pass through membranes, whereas the unbound portion can pass freely through membranes. Thus, any change in the amount of free drug available will affect the distribution of a drug. One of the major sources of protein binding variation is the alteration in plasma albumin concentration, which can result from a number of diseases and physiologic changes. In cirrhosis, the production of albumin is decreased, potentially causing an increased free drug concentration. Protein-losing diseases, such as the nephrotic syndrome, can cause a significant reduction in serum albumin with concomitant increases in free drug concentration. Another important source of variation of free drug concentration in the plasma is the competitive nature of binding between drugs and plasma protein sites. Warfarin, phenytoin, morphine, triamterene, quinidine, diazoxide, furosemide, and clofibrate are a few examples of drugs whose protein binding is related to albumin concentration (15). For these drugs hypoalbuminemia secondary to cirrhosis or nephrotic syndrome increases the percentage of total drug in the blood which is in the free state. For phenytoin, a drop in albumin concentration of 0.1 g/dL results in a 1% increase in free phenytoin. Therefore, more phenytoin is available to interact with receptors resulting in a greater pharmacological response at the same total drug concentration in the blood.

One drug may displace another drug from binding sites on proteins. This again raises the free drug concentration in the blood, resulting in the same problem described above. Oral anticoagulants, oral hypoglycemics, phenylbutazone, and numerous other drugs that are extensively bound to plasma proteins are subject to clinically significant interactions by this mechanism.

ELIMINATION

The major routes of elimination are metabolism by the liver and elimination by the kidney. The liver performs various biochemical alterations of drug molecules leading to a metabolite that is more water soluble and more easily excreted by the kidney. Several

types of metabolites are possible, including those that are more active, less active, have no activity, and toxic compared with the parent compound.

Physiologic factors that can influence metabolism are blood flow to the liver and genetic differences in metabolic activity. Drugs that are highly extracted by the liver are very dependent on blood flow to the liver for their metabolism. Drugs such as lidocaine and theophylline have decreased metabolic clearance in patients with congestive heart failure. This has been attributed to the reduction of blood flow to the liver associated with congestive heart failure (10).

A major factor contributing to the variable rates of metabolism by the liver between individuals is the intrinsic genetic differences in the amount and activity of enzyme systems responsible for drug metabolism. In the case of theophylline, the half-life varies from 1.5 hr to longer than 20 hr. This intrinsic ability to metabolize drugs can be decreased by diseases such as hepatitis and cirrhosis or increased by agents that increase the metabolic activity of these enzyme systems (e.g., phenobarbital or rifampin).

Two important concepts which facilitate the general understanding of elimination are *half-life* and *clearance*. The half-life is the time required for the plasma concentration to decrease by 50% after absorption and distribution are complete. For drugs with first-order elimination it takes five half-lives to reach steady state. Steady state is the point at which the rate of elimination is equal to the rate of administration. This is also the point where the serum concentration is maximal and the maximal pharmacologic response is seen. The following case study illustrates the accumulation of gentamicin to steady state.

Case Study 1.

A patient is given gentamicin 80 mg q. 8 hr. The half-life is found to be 8 hr. Prove that it takes 3 to 5 half-lives to reach steady state. Also show that the amount of drug given is equal to the amount eliminated at steady state.

$t_{1/2}$	Dosage interval	Amt lost		Amt drug in body at end of dosage interval
1	1st	(80) (.5)-40	mg	40 mg
2	2nd	(80 + 40) (.5)-60	mg	60 mg
3	3rd	(80 + 40) (.5)-70	mg	70 mg
4	4th	(70 + 80) (.5)-75	mg	75 mg
5	5th	(75 + 80) (.5)-77.5	mg	77.5 mg
6	6th	(77.5 + 80) (.5)-78.7	mg	78.5 mg
7	7th	(78.7 + 80) (.5)-79	mg	79 mg
8	8th	(79 + 80) (.5)-80	mg	80 mg

Thus at steady state, 80 mg is given and 80 mg is eliminated.

Clearance is the ability of any organ system to extract totally a drug from a given volume of plasma. Total body clearance is the body acting as a whole to eliminate the drug. Major organ systems that are important in this process are the liver and the kidneys. The total clearance is the sum of the individual clearances of the drug by various organs and tissues of the body. Further discussion of clearance can be found in the chapter on protein binding.

Many drugs are not substantially metabolized by the liver; these include digoxin, the aminoglycosides, and the penicillins. Their major route of elimination is by the kid-

neys. Renal clearance is the ability of the kidney to extract a substance from blood and excrete the drug into the urine. Quantitatively, this is defined as the rate of excretion divided by the average concentration of the excreted substance in the plasma. The renal clearance of creatinine is a commonly used index of renal function because this endogenous substance undergoes complete glomerular filtration and is subject to very little renal tubular secretion and reabsorption. The renal clearance of drugs can exceed, be the same as, or be less than creatinine clearance, depending on the degree of glomerular filtration, renal tubular secretion, and reabsorption. The renal clearance of a drug depends on urine pH, renal blood flow, plasma protein binding, age, and renal disease. For drugs dependent on renal elimination, intrinsic renal disease can lead to significant decreases in the amount of drug eliminated per unit time. The renal clearance of a number of drugs, including gentamicin and tobramycin, has been found to be proportional to creatinine clearance, thereby permitting prediction of their renal clearance in patients with kidney disease. This concept is discussed in more detail in the aminoglycoside chapter.

SERUM CONCENTRATIONS AND PHARMACOLOGIC RESPONSES

For agents such as digoxin, phenytoin, gentamicin, quinidine, procainamide, and several other drugs with narrow therapeutic indices, the dosages necessary for optimal therapeutic effects differ widely among patients. When standard dosages of these drugs are used, wide variability in response occurs. In some patients, this may lead to therapeutic ineffectiveness and others may manifest toxicity. The administration of a conventional dose can be satisfactory only when a drug's therapeutic margin is very large and when its full therapeutic potential is not required. For some drugs, the pharmacologic response is easily measured; for example, the prothrombin time is used to measure the effect of warfarin. For other agents, determining the best dosage for individual patients is difficult because the pharmacologic response is not quantifiable in the usual clinical situation. In this situation, the use of serum drug concentrations has become very useful in individualizing drug therapy.

As already noted, enormous differences in relation to the dosage of drug and the intensity of its pharmacologic action are influenced by several factors. The variability of the dose-effect relation among patients is primarily due to individual differences in serum concentration achieved with a given dosage schedule rather than to a different intensity of action associated with the same serum concentration. For many drugs, the relation between the serum concentration achieved and the dosage given is quite variable. This can be attributed to differences in completeness of absorption, Vd, and elimination.

The serum concentration of a drug is in dynamic equilibrium with the tissue receptors of that drug. Thus, it has been found for a number of drugs the serum concentration is a useful guide to the pharmacologic and toxic effect. Measurements of serum concentrations of a drug become useful guides for dosage adjustments only when the therapeutically effective range of serum concentrations has been defined. Table 3 presents a list of major drugs for which this has been accomplished.

Concentrations of these agents below the therapeutic range can exert beneficial effects but are inadequate in most patients. As serum concentrations rise above the therapeutic range, the frequency and severity of toxic effects increase progressively. Some patients may tolerate serum concentrations above the usual therapeutic levels and may

TABLE 3. *Therapeutic ranges of serum concentrations of selected drugs*

Drug	Therapeutic range
Digitoxin	14–30 mcg/liter
Digoxin	0.9–2 mcg/liter
Phenytoin	10–20 mg/liter
Lidocaine	1.5–5 mg/liter
Lithium	0.5–1.3 mEq/liter
Nortriptyline	50–150 mcg/liter
Procainamide	4–8 mg/liter
Quinidine	2–6 mg/liter
Disopyramide	2–4 mg/liter
Gentamicin	4–10 mg/liter (peak) less than 2 (trough)
Tobramycin	4–10 mg/liter (peak) less than 2 (trough)
Amikacin	20–30 mg/liter (peak) less than 10 (trough)
Theophylline	10–20 mg/liter

need concentrations at this level to maintain adequate therapeutic effect. Whenever this is the case, these patients should be monitored closely for side effects.

Phenytoin serves as an example of an agent where serum drug concentration monitoring is essential. When using a standard dosage of 300 mg/day, the serum concentration can vary from 2 to 50 mg/liter. This variability is due to individual differences in the rate of hepatic metabolism of phenytoin. In the vast majority of patients, the effective range of serum concentrations lies between 10 and 20 mg/liter for both the anticonvulsant and antiarrhythmic actions of the drug. Thus, when standard dosages of phenytoin are employed, many patients will be outside the therapeutic range. The side effects of phenytoin correlate with serum concentration. Nystagmus usually occurs between 20 and 30 mg/liter, ataxia between 30 and 40 mg/liter, and mental changes occur at concentrations higher than 40 mg/liter.

The interpretation of serum concentration data depends on several factors. Important considerations include the relationship of the time of the serum concentration and the time of the administered dose, altered pathophysiologic states, and type of assay system employed. Appropriate situations where serum concentration data are useful include checking compliance, underlying disease states that alter pharmacokinetics (such as liver or renal disease), insufficient effect or toxicity, and obtaining serum concentration data to estimate pharmacokinetic parameters for the individual patient. These points are illustrated in the case study that follows.

Case Study 2.

A 70-year-old, 90-kg male with bronchitis and emphysema entered the hospital with severe bronchospasm. A drug history revealed the patient has aminophylline 200 mg q.i.d. prescribed. After admission, the theophylline level was negligible. Pertinent physical findings were abnormal liver function tests and congestive heart failure. The patient was placed on a constant infusion of aminophylline at a rate of 54 mg/hr. Two days after admission, the patient complained of nausea and vomiting and was also found to have a rapid heart rate of 150 beats/min. The theophyl-