Wartak

CLINICAL PHARMACO-KINETICS

A Modern Approach To Individualized Drug Therapy

Clinical Pharmacokinetics

A MODERN APPROACH TO INDIVIDUALIZED DRUG THERAPY

Joseph Wartak

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Preface

Recognition of the clinical value of serum concentrations of potent drugs has led to the development of pharmacokinetics, a new branch of pharmacology aimed at describing the fate of drugs in the body using mathematical methods and computer techniques. Over the past ten years pharmacokinetic methods have been used successfully to interpret serum concentrations of drugs, to individualize dosage regimens, and to refine and confirm therapeutic goals.

The importance of the pharmacokinetic approach to drug dosage has been continuously emphasized in the medical literature, and yet this methodology is little known outside a narrow circle of specialists. This unfortunate situation stems from the facts that pharmacokinetics has not yet been introduced into the educational curricula at medical schools, practicing physicians still consider pharmacokinetics an esoteric branch of pharmacology with little significance to the daily practice of therapeutics, and pharmacokinetics is difficult to learn because it is based on concepts that are deeply rooted in mathematics.

The purpose of this book is to provide the essential theoretical information on pharmacokinetics and to illustrate how pharmacokinetic parameters such as drug clearance, plasma half-life, volume of distribution, and protein binding can be employed for preventing or correcting various problems frequently encountered in drug therapy (e.g., poor response, toxic reactions, drug interactions). Since pharmacokinetics makes an extensive use of mathematical apparatus, with which most medical personnel are not conversant, every effort has been made to provide step-by-step explanations and to support difficult concepts with illustrations, which are more comprehensible than words or mathematical notation.

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Contents

1 The Fate of Drugs in the Body

In order to produce a therapeutic effect, a drug must enter the systemic circulation and be delivered in a sufficient amount to the target cells, tissues, or organs where its molecules combine with specific receptors. Between the time of administration of a drug and its action, various pharmacokinetic and pharmacodynamic processes take place. The pharmacokinetic processes include absorption of the drug from the site of its application, distribution from blood to various tissues, biotransformation in the liver, and excretion by the kidney. The rate and extent of those processes determine the drug concentration in the plasma. The pharmacodynamic processes involve interactions between the drug and the receptors that ultimately produce a given pharmacological effect. The intensity of such an effect is determined mainly by the concentration of the drug in the direct environment of the receptors. Usually, it is not possible to determine drug concentrations at the receptor sites in the person. However, such concentrations are assumed to be proportional to drug concentrations in the plasma so that the latter can be correlated with the time course of drug action.

ABSORPTION OF DRUGS

Most drugs must enter the blood in order to reach specific receptors in the target tissue or organ. The rate at which absorption takes place and the amount of drug being absorbed are determined by the route of administration, the dosage form of a drug, and the physicochemical properties of the drug.

When a drug is given intravenously its absorption is instantaneous and complete. When a drug is given intramuscularly or subcutaneously, its absorption is almost complete, but the rate at which the drug enters the circulation depends upon local blood flow and the state of ionization of the drug. Poor local blood flow and highly ionized (or polar) states of drugs slow the rate of absorption.

When a drug is taken by mouth, both the amount absorbed and the rate of absorption are determined by many factors, especially the physical nature of the dosage form, the presence of food in the stomach, the composition of the gastrointestinal contents, the gastric or intestinal pH, the gastrointestinal motility, the mesenteric blood flow, and the concurrent oral administration of other drugs.

Gastrointestinal absorption of tablets and capsules takes place only when a dosage form disintegrates into small particles and gets dissolved in the gastrointestinal fluids. Since disintegration and dissolution of drugs in liquid dosage forms are already accomplished, the latter are more rapidly absorbed than are tablets and capsules.

The absorption of many drugs from the gastrointestinal tract is impaired by the presence of food, milk, and antacids. Food blocks large surface areas available for absorption, while calcium in dairy products forms insoluble complexes with tetracyclines. The absorption is faster and more complete when a drug is taken on an empty stomach with a glass of water.

Most drugs are weak acids or weak bases, and their diffusion across membranes will be affected by the pH because nonionized compounds pass more readily through membranes. At low pH, acidic drugs are, for the most part, nonionized and are absorbed relatively fast. Basic drugs, on the other hand, are nonionized in a neutral or basic environment. Because the pH values in the gastrointestinal tract vary, different parts will be involved in the absorption of different drugs. Acidic drugs will be absorbed mainly in the stomach because the pH is near 1, while basic drugs will be absorbed mainly in the small intestine where the pH is approximately 5 to 7. For example, aspirin is un-ionized in the acid pH of the stomach and therefore it is well absorbed. However, raising the pH of the stomach by concomitant use of antacids will ionize aspirin and decrease its absorption.

BIOAVAILABILITY OF DRUGS

The term bioavailability refers to the fraction of the dose of a drug that enters the systemic circulation. This fraction can be deter-

mined by comparison of blood levels achieved after similar oral and intravenous doses.

When drugs are injected intravenously, the whole dose is introduced into the systemic circulation. However, when drugs are given by any route other than intravenous injection, the whole dose may never enter the systemic circulation because part of the dose will fail to absorb, or get destroyed by gastric acid, or become metabolized in the intestine wall during the passage of drug molecules from the gut lumen to the systemic circulation. Incomplete absorption is usually a result of poor disintegration and dissolution of tablets and capsules, delayed gastric emptying, diminished surface area of the gut, gastrointestinal disease, or the presence of other drugs, ions (e.g., antacids), or food. Poor disintegration and dissolution of tablets and capsules may be caused by formulation factors (particle size, type and quantity of excipient, compression force).

A major fact that can reduce the bioavailability of certain drugs is extensive metabolism in the liver during the first passage of the drug through that organ. This so-called "first-pass effect" results from the fact that all orally absorbed drugs must enter the liver via the portal vein before reaching the systemic circulation. Drugs such as morphine and lidocaine are so extensively metabolized in the liver and the gut wall that they are ineffective when taken orally. For other drugs such as propranolol, nortriptyline, and alprenolol the first-pass metabolism may vary from 50 to 90%, and high oral doses must be given to overcome those losses.

DISTRIBUTION OF DRUGS

When a drug enters the circulation, it is rapidly diluted and transported by the plasma to the various tissues of the body. Some drug molecules are suspended in the plasma water while others are loosely attached to plasma proteins and blood corpuscles. Only the free drug can move out of the blood into tissues and exert its pharmacological effect. The bound drug is pharmacologically inactive and provides a reserve of drug that replenishes the free drug that moved out of the circulatory bed. When two drugs are given simultaneously and both compete for the same sites on plasma proteins, the one with the higher affinity will be preferentially bound to plasma proteins and more of the other drug will be available in a free form. For example, phenylbutazone, which has a higher affinity than warfarin, will displace warfarin from its binding sites thus increasing the level of free warfarin and potentiating its pharmacological action.

Once a drug enters the circulation, a continuous distribution and redistribution occurs until it is finally eliminated from the body. The rate, sequence, and extent of distribution depends upon many factors: the physicochemical properties of the drug, the cardiac output and regional blood flow, the anatomical characteristics of membranes, the transmembrane electric and pH gradients, and the binding to plasma and tissue protein.

Since cellular membranes are composed of a double layer of lipid molecules that are covered on both sides by a protein coat, the rate of transmembrane movement is increased when the drug is lipid-soluble, nonionized at plasma pH, and has weak binding to plasma proteins. On the other hand, water-soluble and ionized drugs with strong binding to plasma proteins cross various membranes, especially the membrane of the cerebral capillaries, with some difficulty. Consequently, drugs with high lipid-water partition coefficients are taken up by tissues very fast. The rapid distribution of lipophilic drugs is especially pronounced in the central nervous system, which has the highest blood flow rate in relation to tissue mass. Because of this rapid distribution, there is an immediate onset of general anesthesia once an anesthetic agent (e.g., thiopental) enters the systemic circulation.

Some drugs attain a very high level in specific tissues (e.g., digoxin in the heart and muscles, thiopental in fatty tissues) because of their fast and extensive uptake. This so-called sequestration of a drug results in low drug levels in the plasma and a large apparent volume of distribution for the drug.

METABOLISM OF DRUGS

The majority of drugs undergo a variety of chemical reactions in the liver and, to a much lesser extent, in other organs (e.g., intestinal wall, kidney, lungs). Such reactions include oxidation, reduction, hydrolysis, and conjugation (with carbohydrates, amino acids, acetate, sulfate, and methyl groups) and are directed toward the production of metabolites that are more ionized, more water-soluble, and less capable of penetrating cell membranes and being sequestrated in tissues. The more polar or water-soluble a compound becomes, the more readily it is excreted through the kidney and hepato-biliary system. This biotransformation is extremely important because most drugs are lipid-soluble weak electrolytes so that they would be readily reabsorbed through the renal tubule and remain in the body almost indefinitely. For example, a lipophilic drug that is strongly

bound to plasma or tissue protein and not metabolized can easily have the elimination half-life of 100 years.

In general, biotransformation makes a drug inactive. Occasionally, however, drug metabolism will transform the parent drug to another active form. For example, phenacetin is metabolized to paracetamol, phenylbutazone to oxyphenbutazine, and amitriptyline to nortriptyline, all of which are equally active as the parent drugs. In fact, these metabolites have been manufactured as equivalent and usually less toxic drugs than the parent compounds.

The rate of metabolism may be influenced by many factors among which the genetic make-up of the individual and drug interactions are the most important. Metabolism of some drugs, the acetylation of isoniazid being the best example, can proceed at a rapid rate in one population and at a slow rate in another population. A slow rate is due to the deficiency of a specific enzyme because of some genetic defect and results in an increased sensitivity to drugs. For example, in subjects with acetylase deficiency, the speed of acetylation and inactivation of isoniazid is decreased and consequently the usual doses of the drug will produce toxic effects (peripheral neuritis).

The activity of the drug-metabolizing enzymes may be increased or decreased by a wide variety of drugs and other foreign chemicals (e.g., alcohol, benzpyrene derivatives in cigarette smoke, DDT in the environment). Some drugs (especially barbiturates and many anticonvulsants) may stimulate the microsomal drug-metabolizing enzymes in the liver and consequently enhance the detoxification and elimination of other drugs given concurrently. For example, when the patient treated with dicumarol takes phenobarbital, the latter may stimulate the metabolism of dicumarol and consequently lower its plasma levels and diminish anticoagulant activity.

On the other hand, the activity of the drug-metabolizing enzymes may be decreased or inhibited by some drugs, especially allopurinol, monoamine oxidase inhibitors, and chloramphenicol, and consequently the detoxication of other drugs given concurrently will be impaired. The same effect may be brought about by starvation, dietary deficiencies of protein or vitamins, stress, fever, dehydration, or acute liver disease.

EXCRETION OF DRUGS

Most drugs and drug metabolites are excreted in the urine. Some drugs and drug metabolites are excreted into the bile and, subse-

quently, may be absorbed from the intestine and returned to the circulation. This cycle of events, which is called an entero-hepatic shunt, may potentiate and/or prolong a drug's action. Volatile anesthetic agents are eliminated mainly by the lungs.

Most drugs have a molecular weight less than 500 and, therefore, are readily filtered in the glomeruli. Only drugs bound to proteins or of excessively high molecular weight will be unable to cross the glomerular membrane. The final concentration of the drug or its metabolite in the voided urine is determined by how much is passively reabsorbed into the renal tubules and how much is secreted into the lumen of the renal tubules by active transport. Tubular reabsorption depends on factors such as lipid solubility of the drug and urinary pH.

Those drug molecules that are lipid-insoluble and ionized (e.g., digoxin, penicillin, streptomycin) will remain within the tubular fluid and will appear in the urine in high concentrations. Lipid-soluble and nonionized drugs readily diffuse from the tubular fluid into tubule cells and eventually return to plasma. However, they are metabolized by the liver into lipid-insoluble derivatives that are not appreciably reabsorbed.

Reabsorption of drugs that are weak acids or bases also depends upon the pH of the urine. Consequently, urine pH can be intentionally altered by the administration of sodium bicarbonate or ammonium chloride to increase the degree of ionization of some drugs. Thus, alkalinizing the urine will increase ionization of acidic compounds such as aspirin or barbiturates with consequent impairment of their reabsorption resulting in increased excretion. If alkali such as sodium bicarbonate or certain antacids are given together with aspirin, the serum level of salicylate will be lower than if aspirin were given alone. On the other hand, acidification of the urine will increase ionization of basic drugs, such as amphetamine or ephedrine, with consequent impairment of their absorption and increased excretion.

Some acidic drugs such as penicillins, some sulfonamides, and probenecid are also secreted by the renal tubules into the urine. This is an active process that can be inhibited competitively by related compounds. For example, probenecid can be used to inhibit the secretion of penicillin and thus increase its half-life.

2 *Concentration of Drugs in the Blood*

Drugs administered by enteral or parenteral routes will enter into the systemic circulation where their concentration can be measured, graphed against time, and correlated with their therapeutic effects. For most drugs, the time course of drug concentrations in the plasma correlates well with the onset, intensity, and duration of the therapeutic effect. Consequently, sampling the plasma at intervals during therapy can be helpful in establishing dosage schedules that are likely to produce the desired drug concentrations and thus reduce the risk of ineffectiveness or toxicity. This approach is especially important when the drugs' therapeutic plasma concentrations are within a narrow range or when there is no simple objective measure of the response to a drug.

SINGLE-DOSE CONCENTRATION CURVES

When a single dose of a drug is given by mouth or by some other extravascular route, the drug appears in the plasma a short time after the administration and its concentration rises steadily until the peak level is reached. Once the drug enters the circulation, it is subject to biotransformation and elimination, which tend to lower the plasma concentration. However, during the initial period, the rate of absorption exceeds the rate of elimination. When the peak level is reached, both the absorption and elimination rates are the same. Thereafter,

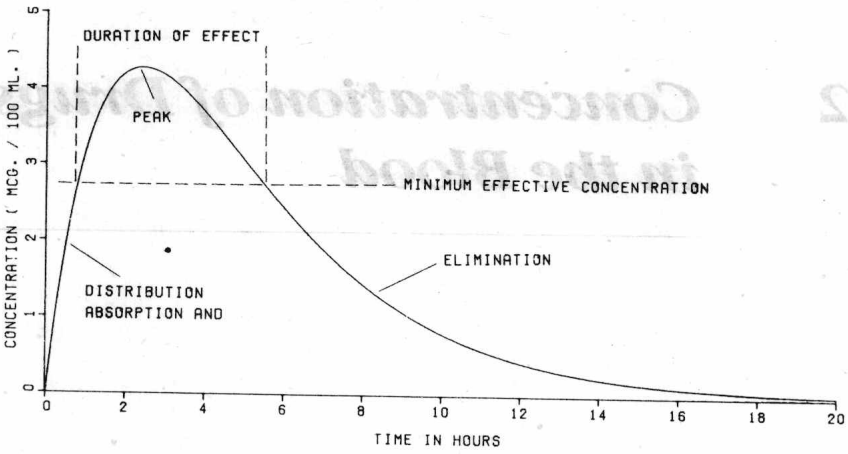

Figure 1. Computer plot to illustrate an idealized time course of plasma concentrations of a hypothetical drug following extravascular administration of a single dose.

as the elimination rate exceeds the absorption rate, the plasma drug concentration begins to fall.

When drug concentration in the plasma following a single dose is measured at frequent time intervals and plotted on graph paper, a characteristic curve is obtained (Fig. 1). The important features of such a curve are the ascending limb, the peak, and the descending limb.

The ascending limb of the plasma concentration curve reflects drug absorption into systemic circulation and its distribution to tissues. The slope of this limb reflects the rate of such processes so that the steeper the slope the more rapidly the drug is absorbed into systemic circulation and/or the more slowly the drug is distributed to tissues. The peak of the curve reflects the maximum concentration reached by a single dose. The descending limb of the curve reflects drug metabolism and excretion. The slope of this limb represents the rate of such processes so that the steeper the slope the more rapidly the drug is metabolized and/or excreted. It should be realized, however, that elimination starts as soon as a minute quantity of the drug has been absorbed. Similarly, absorption does not cease at the peak concentration but continues for some time at a very slow rate. The slope and length of the ascending and descending limbs, as well as the height of the peak and the time of its occurrence, depend upon the

rate of absorption and elimination that are characteristic for a given drug, although they may be significantly influenced by the functional status of the patient's organs (e.g., kidney, liver), and to a lesser extent by the route of administration. Various patterns of plasma drug concentration curves obtained under different conditions are discussed in Chapter 11.

The onset and duration of therapeutic effects can be correlated with plasma concentrations in the following way. In general, a therapeutic effect starts when a drug reaches its minimum effective concentration (MEC) in the plasma and persists for as long as the plasma level is above the MEC. In addition, the intensity of therapeutic effects for many drugs will be proportional to the height of the plasma concentration curve above the MEC, and the maximal intensity (or the peak effect) will occur at the time of peak concentration.

THE HALF-LIFE OF DRUGS

When a drug is administered by rapid intravenous injection, the maximum concentration in the blood is reached at once and immediately begins to decline. The profile of such a decline can be depicted by periodically assaying samples of blood and plotting the results on graph paper.

When rectangular graph paper is used, the blood level profile is represented by a parabola or an exponential curve (Fig. 2, top). Such a curve shows a steep slope at the beginning, a less steep slope in the middle, and becomes almost flat at the end. This is determined by the fact that when the amount of drug in the blood is large, the elimination is fast and when the amount of drug in the blood is small the elimination is slow. In other words, the slope of the plasma concentration–time curve represents the rate of drug elimination, and, at any time, such a rate is proportional to the actual amount of drug in the blood at that time.

When semilogarithmic paper is used, a drug's concentration in the blood plotted against time is represented by a straight line, which is more convenient for some calculations (Fig. 2, bottom).

In clinical medicine, the disappearance of a drug from the plasma is commonly expressed in terms of the drug's half-life ($t_{1/2}$). This is the time required for the plasma concentration to decrease to one-half of its initial value. By examining Figure 2, we find that one-half of the initial concentration is 5 μg/100 ml and the time it takes for the blood concentration to fall to this level is 2 h. The same time