Pharmacokinetic Basis for Drug Treatment

Edited by

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Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data
Main entry under title;

Pharmacokinetic basis for drug treatment.

Includes bibliographical references and index.
1. Pharmacokinetics. 2.Chemotherapy. I. Benet, Leslie Z. II. Massoud, Neil. III. Gambertoglio, John G. [DNLM: 1. Drug therapy. 2. Pharmacology, Clinical. QV 38 P532]
RM301.5.P46 1983 615.7 83-9512
ISBN 0-89004-874-6

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Preface

In 1973, Mitenko and Ogilvie attempted to develop a logical theophylline dosage regimen based on the drug's established pharmacokinetics and pharmacodynamics. Although the temporary acceptance of the recommendations by the general medical community represented a great step forward for clinical pharmacokinetics as a science, the acceptance proved to be premature and reverberations are still being felt today. The problem was that their recommendations were appropriate only for nonacutely ill asthmatics. An enormous variability in the true patient population was soon found, and patients were often seriously overdosed or underdosed. In time, subpopulations with distinct physiologically altered pharmacokinetics were identified, and an entirely new set of recommendations presently exists for theophylline dosage among these populations.

At any point in the history of health care, our knowledge was considered to be quite extensive; however, in perspective, the knowledge of yesterday seems to have been very limited, just as today's knowledge can be expected to seem one day as such. It is apparent that a great void exists and, as a result, there continues to be a need to expand and accumulate knowledge and information. In this expansion, clinical pharmacokinetics has evolved as a new science in health care. As such, it often has given answers that were ambiguous or, as with the initial theophylline dosage guidelines, highly questionable. For this reason, in the development of this science, one must always question ideas and constantly challenge assumptions made in the process of developing this field. Fundamental in applying basic scientific and mathematical concepts to patient care is an appreciation of the physiologic constraints placed on these concepts and an appreciation of how disease and/or physiologic changes can further affect these constraints.

This book covers pharmacokinetics in all the common diseases, as well as drug clearance, and altered plasma protein binding. It provides values for patients with specific diseases, along with normal values obtained from volunteers. It is comprehensive, with chapters discussing aspects of pharmacokinetics in regard to the care of pediatric and geriatric patients, the effects of smoking and pregnancy, and the placental transfer of drugs.

To date, this is the only book to provide the pharmacokinetic concepts and relevant parameters necessary to design more tailored dosage regimens for specific patient populations. This book will be of interest to pharmacists, pharmacologists, and prescribing physicians.

Acknowledgments

The editors wish to acknowledge the following individuals: Dr. G. O. Barbezat of the University of Otago, New Zealand; Dr. Jorden L. Cohen of the University of Southern California; Dr. Gedy Gudauskas at the Cancer Control Agency of British Columbia; Dr. Martha Harkey at the French Hospital Medical Center, San Francisco; Dr. John H. Holbrook of the University of Utah; and Dr. Beatrice Krauer at the Hospital Cantonal, Geneva. The editors also acknowledge their colleagues at the University of California, San Francisco: Drs. Donald Alexander, Nicholas H. G. Holford, Robert H. Levin, Diane Dan-Shya Tang-Lui, Michael E. Winter, and Robert A. Upton. All of the above individuals provided critical evaluations of specific chapters in this text.

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Contents

Pharmacokinetic Basis for Drug Treatment, edited by L.Z. Benet et al., Raven Press, New York © 1984

Chapter 1
Pharmacokinetics

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Drug treatment, or therapeutics, has historically been associated with pharmacodynamics, the study of "what the drug does to the body." It has long been recognized that disease states may modify the relationship between drug dosing and both drug efficacy and drug toxicity. More recently, it has become obvious that disease states may modify pharmacokinetics and/or pharmacodynamics, and that it is impossible to isolate the particular effect of a disease on these two processes without investigating the time course of a drug and its metabolites in the patient. The aim of this volume is to provide a comprehensive review and critical compilation of the information available concerning the effects of disease states on pharmacokinetics, that is, the information which describes "what the body does to the drug." This information may then serve to provide a rational basis for the initial adjustment of drug treatment in a particular patient. Neither the title of this volume, nor the encyclopedic compilation of clinical pharmacokinetic information provided should be interpreted as implying that the effects of disease on pharmacodynamics are unimportant. However, at this point in time, few studies have addressed the separation of the effect of disease on pharmacokinetics and pharmacodynamics. When available, the information is provided in the chapters which follow.

When a clinician prescribes a drug, and a patient takes it, their fundamental concern is with the beneficial effect of the agent on the patient's disease. However, as illustrated in Fig. 1, several processes are interposed between administration of the dose, the resulting plasma or blood concentration, and the appearance of the drug's therapeutic effect. Physiological processes determine how rapidly, at what concentration, and for how long the drug will appear at the target organ. Three steps shown in Fig. 1—bioavailability, distribution, and clearance (loss)—represent three major pharmacokinetic variables (1). In most cases, the drug will be administered to the body via the most convenient site that meets the requirements for speed and completeness of availability. The pattern of the concentration/time curve measurable in the blood is a function of the bioavailability, distribution, and loss factors. The various chapters in this book will address how each of the pharmacokinetic factors may be modified in disease (see Fig. 1).

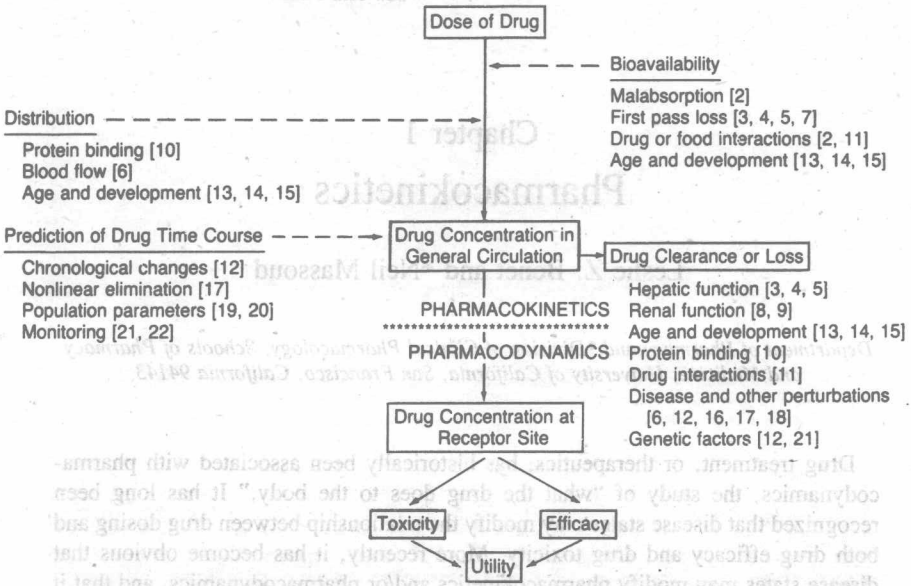

FIG. 1. Schematic interrelationship of pharmacokinetics and pharmacodynamics *(above and below starred line)* in the dose–utility paradigm. Numbers in brackets refer to chapters in this volume where pharmacokinetic concepts are discussed.

Pharmacokinetics is the mathematical relationship that exists between the dose of a drug and the concentration of the drug in a readily accessible site in the body (e.g., plasma or blood). Pharmacodynamics extends this relationship to the correlation between measured concentrations of drug and the pharmacologic effect. This mathematical relationship has been documented for many drugs (2,3) (see Appendixes A–C), although for some drugs, no direct or simple relationship has been found between pharmacologic effect and plasma or blood concentrations. In most cases, the concentration of drug in the general circulation will be related to the concentrations of drug at its site(s) of action (Fig. 1). The drug at the site of action may then elicit a number of pharmacologic effects. These pharmacologic effects can include the desired clinical effect or one or more toxic effects, and in some cases there may be effects unrelated to either the desired effect or toxicity of the drug. The clinician must balance the toxic potential of a particular dose of a drug with its efficacy in determining the utility of the drug.

Pharmacokinetics and pharmacodynamics play roles in the dose–efficacy scheme by describing the quantitative relationship between drug efficacy and dose by means of measurements of drug concentrations in various biological fluids. The importance of pharmacokinetics in patient care rests on the improvement in drug efficacy that can be attained when measurements of drug concentrations in the general circulation are combined with traditional methods of predicting drug dosages (see Chapters 21 and 22). With knowledge of the pharmacokinetic profile of a particular medication and the relationship between efficacy and drug concentration measurements, the

clinician can take into account the various pathological and physiological features that make a particular patient different from the normal individual in responding to a dose of the drug. This will be especially important for a drug with a narrow therapeutic index (e.g., digoxin) where there is only a small difference between the concentration producing therapeutic benefit and the concentration that will produce toxic manifestations. Application of the principles presented in this and subsequent chapters will be of further value in cases where the response is inadequate, where target concentrations may not have been achieved, or in an overdose situation.

PHARMACOKINETIC PARAMETERS

The various pathological and physiological variables that dictate dosage adjustment in individual patients do so by modifying specific pharmacokinetic parameters. The two basic independent parameters are clearance, a measure of the body's ability to eliminate drug, and volume of distribution, a measure of the apparent space in the body available to contain the drug.

CLEARANCE

Clearance is the most important concept to be considered in defining a rational drug dosage regimen. In most cases the clinician would like to maintain steady state drug concentrations within a known therapeutic range (see Appendixes A–C). The steady state will be achieved when the rate of drug elimination equals the rate of input:

$$\text{Dosing rate} = CL \cdot C_{ss} \tag{1}$$

Thus, if the desired steady state concentration (plasma or blood) is known, the clearance value in that patient will dictate the dosing rate.

Drug clearance principles are similar to the clearance concepts in renal physiology, in which creatinine clearance is defined as the rate of elimination of the creatinine in the urine relative to the plasma creatinine concentration (see Chapter 8). At the simplest level, clearance of a drug is the rate of elimination by all routes relative to the concentration of drug in any biologic fluid:

$$CL = \text{rate of elimination}/C \tag{2}$$

It is important to remember that clearance does not indicate how much drug is being removed but rather the volume of blood or plasma which would be completely cleared of drug if it were present. Clearance can thus be expressed as a volume per unit of time.

Clearance *(CL)* is usually further defined as blood clearance *(CL_b)*, plasma clearance *(CL_p)*, or clearance based on unbound or free drug concentration *(CL_u)*, depending on the concentration measured (C_b, C_p, or C_u).

In Appendix B, the plasma clearance for ampicillin is reported as 270 ml/min, with 90% of the drug excreted in the urine unchanged. In other words, the kidney is able to completely remove this drug at a rate of approximately 240 ml of plasma

per minute. Because clearance is usually assumed to remain constant in a stable patient, the rate of ampicillin elimination will depend on the concentration of drug in the plasma, as described by Eq. 2. Propranolol is cleared at a rate of 800 ml/min, almost exclusively by the liver. In this case, the liver is able to remove the drug from 800 ml of plasma per minute. For the drugs listed in Appendix B, one of the highest plasma clearance values is for imipramine, 1,400 ml/min, a value often exceeding plasma flow to the liver, the dominant organ of elimination for this drug. However, because this drug apparently partitions readily into red blood cells ($C_{rbc}/C_p = 2.7$), the amount of drug delivered to the excretory organ is considerably higher than plasma flow indicates. The relationship between plasma and blood clearance at steady state is given by:

$$\frac{CL_p}{CL_b} = \frac{C_b}{C_p} = 1 + H\left(\frac{C_{rbc}}{C_p} - 1\right) \quad (3)$$

One may solve for imipramine clearance in blood by substituting the red blood cell to plasma concentration ratio and the average value for the hematocrit ($H = 0.45$). Then, imipramine clearance, when measured in terms of blood concentration (800 ml/min) is in the physiologic range of blood flow measurements. Thus, like the volume of distribution (to be explained later in this chapter), the plasma clearance may assume proportions that are not "physiologic." A drug with an extremely low plasma concentration that is concentrated in the red blood cells (e.g., mecamylamine) can show a plasma clearance of tens of liters per minute. However, if blood concentration is used to define clearance, the maximum clearance possible is equal to the sum of blood flow to the various organs of elimination (Table 1) (4). For a drug eliminated solely by the liver, blood clearance is therefore limited by the flow of blood to that organ, approximately 1,500 ml/min.

It is important to note the additive character of clearance. Elimination of drug may occur as a result of processes occurring in the kidney, the liver, and other organs. Dividing the rate of elimination at each organ by a concentration of drug (e.g., plasma concentration) will yield the respective clearance at that organ. Added together, these separate clearances will equal total systemic clearance:

$$CL_{renal} + CL_{hepatic} + CL_{other} = CL_{systemic} \quad (4)$$

The example provided in Eq. 4 indicates that the drug is eliminated by liver (see Chapters 3 and 4), kidney (Chapters 8 and 9), and other tissues and that these routes of elimination are additive except for drugs additionally removed by the lung (see Chapter 7). Other routes of elimination could include saliva (Chapter 21), sweat, partition into the gut (see Chapter 2), and additional sites of metabolism such as hydrolysis in blood or muscle.

The two major sites of drug elimination are the kidney and liver. Clearance of drug detected unchanged in the urine is represented by renal clearance. Within the liver, drug elimination occurs via biotransformation of unchanged drug to one or more metabolites (see Chapters 3, 4, 21) and/or excretion of unchanged drug into the bile (see Chapter 5). For most drugs, clearance is constant over the plasma or blood concentration range encountered in clinical settings (linear): that is, elimi-

TABLE 1. *Volumes and blood supplies of different body regions for a standard man*[a,b]

Tissue	Vol. (liters)	Blood flow (ml/min)	Blood flow (ml/100 ml tissue × min)	Vol. of blood in equilibrium with tissue (ml)
Adrenals	0.02	100	500	62
Kidneys	0.3	1,240	410	765
Thyroid	0.02	80	400	49
Gray matter	0.75	600	80	371
Heart	0.3	240	80	148
Other small glands and organs	0.16	80	50	50
Liver plus portal system	3.9	1,580	41	976
White matter	0.75	160	21	100
Red marrow	1.4	120	9	74
Muscle	30.0	300/600/1,500	1/2/5	185/370/925
Skin				
Nutritive	3.0	30/60/150	1/2/5	18/37/92
Shunt		1,620/1,290/300	54/43/10	
Nonfat subcutaneous	4.8	70	1.5	43
Fatty marrow	2.2	60	2.7	37
Fat	10.0	200	2.0	123
Bone cortex	6.4	0	0	0
Arterial blood	1.4	—	—	—
Venous blood	4.0	—	—	—
Lung parenchymal Tissue	0.6	—	—	—
Air in lungs	2.5 + half tidal volume	—	—	1,400[c]
				999/795/185[d]
Total	70.0[e]	6,480		5,400

[a]Data compiled by Dedrick and Bischoff (5), from mean estimates of Mapleson (6).
[b]Standard man = 70-kg body weight, 1.73 m² surface area, 30–39 years old.
[c]Arterial blood.
[d]Skin-shunt venous blood.
[e]Excluding the air in the lung.

nation is not saturable, and the rate of drug elimination is directly proportional to concentration (Eq. 2). For drugs that exhibit saturable or dose-dependent elimination (nonlinear), clearance will vary depending on the concentration of drug that is achieved (see Chapters 17 and 21). Dosage adjustments with such drugs are more complex.

A further definition of clearance is useful in understanding the effects of physiologic and pathologic variables on drug elimination, particularly with respect to an individual organ. The rate of elimination of a drug by an individual organ can be defined in terms of the blood flow entering and exiting from the organ and the concentration of drug in the blood. The rate of presentation of drug to the organ is the product of blood flow and entering drug concentration ($Q \cdot C_A$), and the rate of exit of drug from the organ is the product of blood flow and exiting drug concentration ($Q \cdot C_V$) (Fig. 2). The difference between these rates at steady state is the rate of drug elimination.

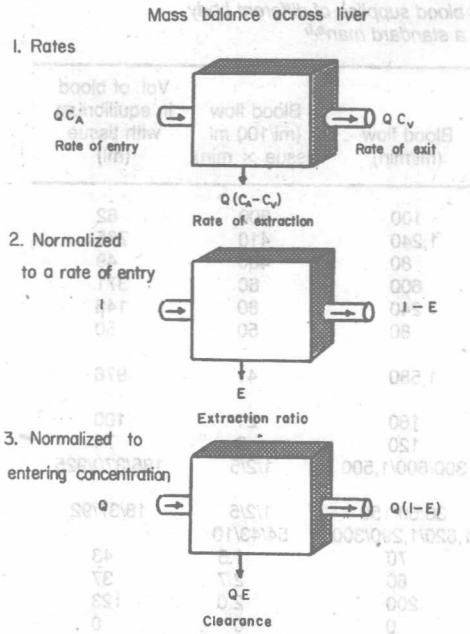

FIG. 2. The principles of mass balance can be used to illustrate the extraction of a drug in the liver. **1:** The difference between the rates in and out of the organ is the *rate of extraction.* **2:** Normalizing the rates to the rate of entry provides a measure of the fraction extracted, the *extraction ratio.* **3:** Normalizing the rates to the entering drug concentration gives the volume of entering blood from which the drug appears to be extracted, the *clearance.* (From Tozer, ref. 7, with permission.)

$$\text{Rate of elimination} = Q \cdot C_A - Q \cdot C_V \tag{5}$$

(At steady state the amount of drug reaching the systemic circulation will equal the amount being eliminated.) Dividing Eq. 5 by concentration of drug entering the organ of elimination (C_A), an expression for organ clearance of drug is obtained:

$$CL_{organ} = \frac{Q \cdot C_A - Q \cdot C_V}{C_A} \tag{6a}$$

$$= Q \frac{C_A - C_V}{C_A} = Q \cdot E \tag{6b}$$

As shown in Eq. 6b, the expression $(C_A - C_V)/C_A$ can be referred to as the extraction ratio of the drug (E).

The concepts developed in Eqs. 6a and 6b have important implications for drugs that are eliminated by the liver. Consider a drug that is efficiently removed from the blood by hepatic processes. In this instance, the concentration of drug in the blood leaving the liver will be low, the extraction ratio will approach unity, and the clearance of the blood will become limited by hepatic blood flow. Drugs highly extracted by the liver (Table 2) (see Chapters 3 and 4) are restricted in their rate of elimination not by intrahepatic processes but by the rate at which they can be transported in the blood to hepatic sites of elimination. The concepts embodied in Eqs. 5 and 6 can be derived from consideration of mass balance of a drug across an eliminating organ at steady state. However, simple expressions for clearance,

TABLE 2. *Selected drugs with high (>0.5) and low (<0.3) hepatic extraction ratios*[a]

Low	High
Acetaminophen	Aldosterone
Amobarbital	Alprenolol
Antipyrine	Arabinosyl cytosine
Azapropazone	Bromosulfophthalein
Chloramphenicol	Chlormethiazole
Chlordiazepoxide	Desipramine
Chlorpromazine	Hydrocortisone
Clindamycin	Imipramine
Dapsone	Indocyanine green
Diazepam	Isoproterenol
Digitoxin	Labetalol
Ethchlorvynol	Lidocaine
Griseofulvin	Lorcainide
Hexobarbital	Meperidine
Isoniazid	Metoprolol
Lincomycin	Metyrapone
Lorazepam	Morphine
Minocycline	Nitroglycerin
Oxazepam	Nortriptyline
Phenobarbital	Pentazocine
Phenytoin	Phenacetin
Phenylbutazone	Phenylephrine
Prednisolone	Propranolol
Probenecid	Propoxyphene
Quinidine	Salicylamide
Salicylic acid	Verapamil
Sulfadimethoxine	
Theophylline	
Thiopental	
Tolbutamide	
Warfarin	

[a]These drugs primarily undergo hepatic elimination. For more specific information, see Chapters 3 and 4. Adapted from Benet and Sheiner (2) and Tozer (7,8).

blood flow, and extraction cannot account for the full complexity of hepatic or renal drug elimination. For example, these equations do not account for drug protein binding to blood and tissue components, nor do they permit an estimation of the intrinsic ability of the liver or kidney to eliminate a drug in the absence of limitations imposed by blood flow (see Chapters 10 and 11, and 3, 4, 8, and 9, respectively). To extend the relationships of Eq. 6 to include expressions for protein binding and intrinsic clearance, it is necessary to formulate a model to describe organ elimination of drugs. The most straightforward and most commonly employed model relating the extraction ratio to physiologic parameters is the so-called venous equilibration or well-stirred model (9,10) which assumes that the unbound drug concentration leaving the organ is equal to the unbound concentration inside the organ (Fig. 2) and that the intrinsic ability to metabolize or clear drug (CL'_{int}) is equal to the rate of elimination divided by the unbound concentration in the organ. The clearance (with respect to blood concentration) for the eliminating organ then becomes