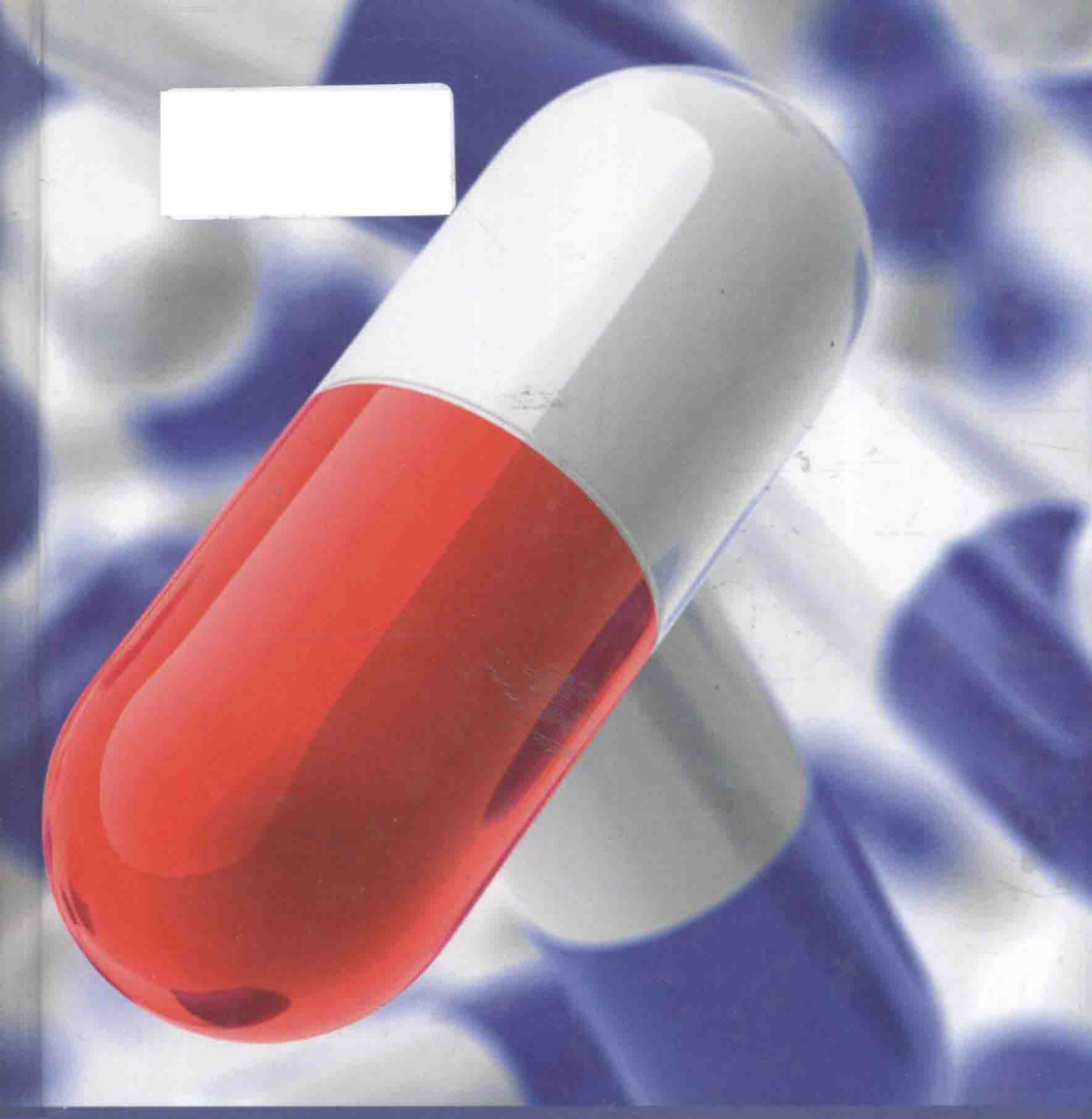

An Integrated Study of Drug Metabolism

Erica Helmer

Essential Pharmacokinetics

A Primer for Pharmaceutical Scientists

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Essential Pharmacokinetics

A Primer for Pharmaceutical Scientists

For her love and support, this textbook is dedicated
to my wife, Hanna Lilja

Preface

Pharmacokinetics is the study of drug kinetics within the body, including drug absorption, distribution, metabolism, and excretion. Pharmacokinetics is most commonly used in clinical situations to enhance the therapeutic efficacy of a patient's drug therapy. However, pharmacokinetics can also be applied in drug design and in the testing of formulations and novel drug delivery systems, as well as in quality evaluations of drug products. This book describes the mathematics used in the mammillary model, which is the most common compartmental model used in pharmacokinetics, and explains how pharmacokinetics can be applied in pharmaceutical product development. This book not only explains the basic concepts of pharmacokinetics and its clinical applications but also how, for example, the physicochemical properties of drugs such as their lipophilicity and aqueous solubility affect their pharmacokinetics, the relationships among Lipinski's rule of five, the biopharmaceutics classification system (BCS), and pharmacokinetics, and the pharmacokinetics of soft drugs and prodrugs. The pharmacokinetics of pharmaceutical excipients and how the excipients affect drug pharmacokinetics are also discussed. The text describes the effects of the routes of administration on drug pharmacokinetics. Numerous equations, practical examples, figures, and problems, with answers, have been included to facilitate self-study.

Contents

Chapter 1

Introduction

Chapter Outline

Although the concept of drug absorption, distribution and elimination has been known for over 150 years [1] the term "pharmacokinetics" was first introduced in 1953 by Friedrich Hartmut Dost in his book "Der Blütspiege: Kinetic der Konzentrationsabläufe in der Krieslaufflüssigkeit" [2,3]. Later Perl [4], Nelson [5], Krüger-Thiemer [6], Wagner [7,8], Garrett [9,10], Rowland [11], Gibaldi [12,13], Riegelman [14], Levy [15], and numerous other scientists introduced the various pharmacokinetic methods and terms, giving us the science of pharmacokinetics as it is today [1].

1.1 SOME BASIC CONCEPTS

A drug proceeds through a distinct pathway from mixing the active pharmaceutical ingredient (API) with excipients to forming the drug product to the therapeutic effect (Figure 1.1). For example, a propranolol tablet is formed by compressing a mixture of the API (i.e., propranolol hydrochloride) and various excipients such as lactose into a tablet. Tablets are one of several different propranolol drug products. Other known propranolol products include oral solutions and solutions for parenteral injection. Following oral administration (sometimes referred to as *per os* or *per oral* [PO] administration), the tablet disintegrates, and solid propranolol dissolves in the aqueous fluid of the gastrointestinal (GI) tract. The dissolved propranolol molecules are then absorbed into the general blood circulation and distributed throughout the body. The drug is partly metabolized and excreted from the body, but a small fraction of the drug, which is a β-blocker, reaches the target site, where its binds to receptors (e.g., β-adrenergic receptors), causing vasodilatation (which is the pharmacologic response) that leads to lowering of blood pressure (which is the therapeutic effect). *Pharmacokinetics* is the kinetics of

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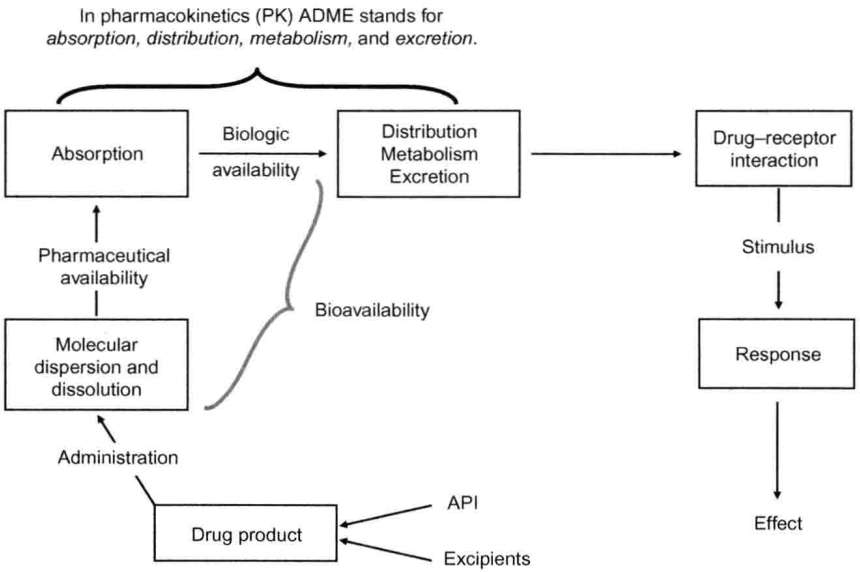

FIGURE 1.1 The drug pathway when, for example, administered orally.

drug absorption, distribution, metabolism, and excretion (ADME). All of these four criteria influence the levels and kinetics of drug exposure to tissues and thus influence the performance and pharmacologic activity of the compound as a drug. ADME profiling and toxicology screening are some of the most important research activities in the drug discovery and development process. ADME and toxicologic (ADME/Tox) properties determine the "druggability" of new chemical entities (NCEs). *Biopharmaceutics* describes how the physicochemical properties of drugs, the pharmaceutical dosage forms, and the routes of drug delivery affect the rate and extent of drug absorption into the body. *Pharmacodynamics* is the science that describes the relationship between the drug concentration at the receptor and biological activity (i.e., pharmacologic response or drug effect).

After oral administration, the drug is absorbed from the GI tract into the body (Figure 1.2). In general, some fraction of the drug is then metabolized and the metabolites excreted through urine, but a fraction of the drug may also be excreted unchanged through urine.

Bioavailability represents the drug fraction that reaches the systemic blood circulation after, for example, oral administration. Bioavailability can be divided into *pharmaceutical availability* and *biologic availability*. If propranolol is completely released from a tablet and dissolved in the aqueous GI fluid, the drug is said to have 100% pharmaceutical availability. Aqueous propranolol solution has 100% pharmaceutical availability (F_{pharm}). However, propranolol undergoes first-pass metabolism and thus its biologic availability (F_{bio}) after

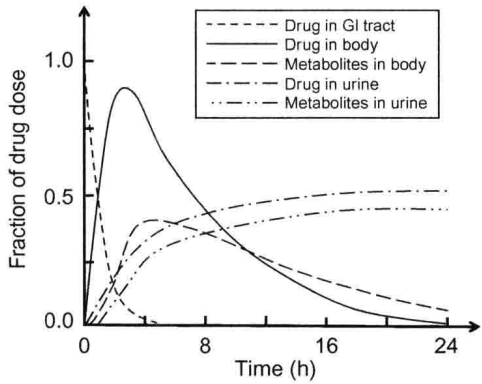

FIGURE 1.2 Schematic drawing showing the course of a drug and its metabolites after oral administration, expressed as a fraction of drug dose, within the body as intact drug and metabolites as well as in the GI tract and urine.

oral administration is frequently about 75%. Consequently, the bioavailability (F) of propranolol solution will be only about 75%:

$$F = F_{\text{pharm}} \times F_{\text{bio}} = 1.00 \times 0.75 = 0.75 \tag{1.1}$$

If the pharmaceutical availability of propranolol in a tablet is 50% and the biologic availability is 75%, the bioavailability of the propranolol tablets will be 37.5%:

$$F = F_{\text{pharm}} \times F_{\text{bio}} = 0.50 \times 0.75 = 0.375 \tag{1.2}$$

Drugs have 100% bioavailability when they are administered through intravenous (IV) injection, that is, the entire drug dose enters the general blood circulation. *Minimum effective concentration* (MEC) is the minimum plasma concentration of a drug needed to achieve sufficient drug concentration at the receptors to produce the desired pharmacologic response, if drug molecules in plasma are in equilibrium with drug molecules in the various tissues (Figure 1.3). *Minimum toxic concentration* (MTC) is the minimum drug plasma concentration that produces a toxic effect. *Onset time* is the time from administration that is required for a drug to reach its MEC. *Duration* of drug action is the difference between the onset time and the time when the drug concentration declines below MEC (Figure 1.3).

After oral administration, the drug is absorbed from the GI tract into the general blood circulation, where it reaches maximum plasma concentration (C_{max}) at time (t) equals t_{max}. Then the concentration declines as a result of metabolism and excretion of unmetabolized drug. The *therapeutic concentration range* (or *therapeutic window*) of a drug is the concentration range from the MEC to the MTC. In animal studies, the *therapeutic index* (TI) is the lethal dose of a drug for 50% of the animal population (LD_{50}) divided by the minimum effective dose for 50% of the population (ED_{50}). In humans, TI is

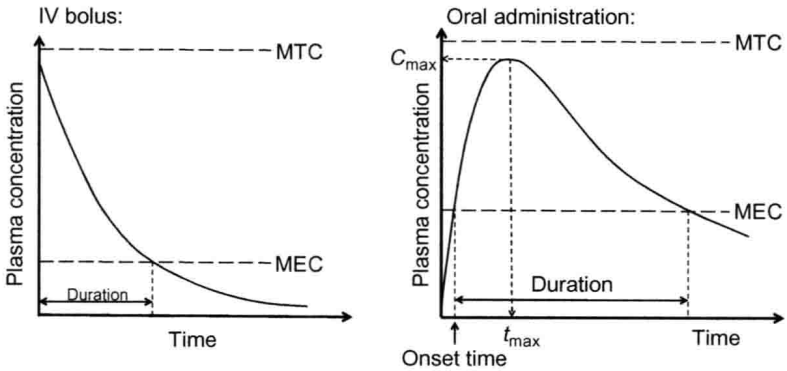

FIGURE 1.3 Drug plasma concentration–time profile of a drug after IV bolus injection and oral administration.

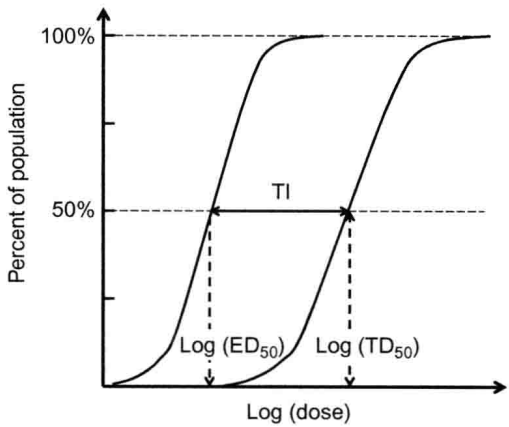

FIGURE 1.4 Drug dose–response relationship for producing the desired therapeutic effect and a toxic side effect (see section 5.3).

frequently defined as the ratio of the dose that produces toxicity in 50% of the population (TD_{50}) divided by ED_{50} (Figure 1.4):

$$\text{In animals:} \quad TI = \frac{LD_{50}}{ED_{50}} \tag{1.3}$$

$$\text{In humans:} \quad TI = \frac{TD_{50}}{ED_{50}} \tag{1.4}$$

1.2 PHARMACOKINETIC MODELS

Various types of pharmacokinetic models are used to describe drug absorption, distribution, metabolism, and elimination from the body (i.e., ADME). There are three basic types of pharmacokinetic modes: (1) *compartmental*

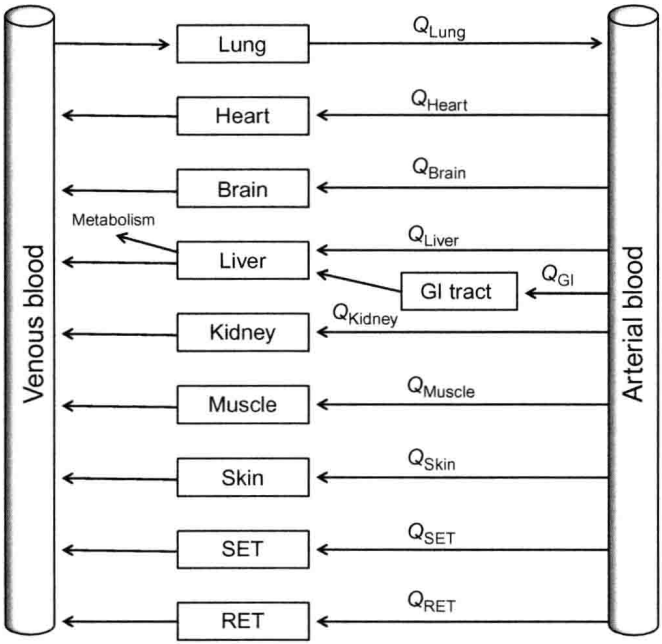

FIGURE 1.5 A physiologic-based pharmacokinetic model, in which compartments are used to represent different organs or group of tissues. Q is the rate of blood flow to the tissue, SETs are slowly equilibrating tissues, and RETs are the rapidly equilibrating tissues.

models, where a compartment represents a group of tissues that have similar affinity to the drug; (2) *physiologic-based pharmacokinetic models*, which apply physiologic parameters such as blood flow and drug partition into tissues; and (3) *noncompartmental models*, which use time and drug concentration averages. In compartmental models, groups of tissues that have similar blood flow and drug affinity are represented as single compartments. The compartments do not represent any specific anatomic region within the body. Uniform drug distribution is assumed within each compartment, and simple first-order rate equations are used to describe the transport of drug into and out of the compartment. Since the drug can enter and leave the body, the models are characterized as "open" models. The *caternary model*, in which the compartments are arranged like train wagons, and the *mammillary model*, which consists of one central compartment connected to peripheral compartments, are examples of compartmental pharmacokinetic models. The most common pharmacokinetic model in humans, and the only one discussed in this book, is the mammillary model.

Ideally, each and every tissue and body organ should be represented by one compartment, but the complexity of the human anatomy and physiology makes it virtually impossible. However, in physiologic-based pharmacokinetic models, some organs or tissues are represented by single compartments, whereas others are grouped into paired compartments (Figure 1.5). The blood

flow (Q) to each organ, as well as the drug uptake to the organ, has to be known. Physiologic-based pharmacokinetic models are sometimes used to describe drug pharmacokinetics in laboratory animals, but they are seldom used to describe the pharmacokinetics of drugs used in humans.

Although compartmental pharmacokinetic methods estimate the drug concentration–time profile with the use of kinetic models, noncompartmental methods estimate the exposure to a drug by estimating the area under the curve of a drug concentration–time profile by using, for example, the trapezoidal method. Other parameters such as biologic half-life ($t_{½}$) of a drug, its clearance, C_{max} and t_{max} can also be estimated. Noncompartmental analysis of pharmacokinetic data does not assume any specific compartmental model. It produces results that can sometimes be acceptable in bioequivalence studies, but the method only provides estimations and results that are difficult to validate.

1.3 POPULATION PHARMACOKINETICS

Considerable pharmacokinetic differences can exist among patients (interindividual variability). Such variations can be caused by genetic influences, environmental influences, gender, drug–drug interactions, age, and body weight. Also, diseases can cause a patient to respond differently to a drug from 1 day to another (intraindividual variability). *Population pharmacokinetics* is the study of the sources of such variability. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors such as kidney and liver functions that cause changes in the drug dose–concentration relationship and the extent of these changes so that dosage can be appropriately modified. Due to inter- and intraindividual variability, the administration of drugs with a narrow therapeutic concentration range needs to be individualized. *Therapeutic drug monitoring* (TDM) refers to individualization of drug dosage by maintaining drug plasma concentration within the therapeutic concentration range. Frequently, such monitoring is based on clinical observations and determination of drug plasma concentrations. Therapeutic concentration ranges of selected drugs are displayed in Table 1.1.

Pharmacokinetics is used to optimize the administration and the therapeutic effects of drugs, as well as the design and evaluation of drug dosage forms. For example, pharmacokinetics can be used to:

1. Calculate loading and maintenance drug doses. The *loading dose* is a large initial dose given to achieve therapeutic drug levels from the beginning; a *maintenance dose* is then given at fixed intervals to keep drug concentrations within the therapeutic range.
2. Calculate drug dosage regimen. The dosage regimen is a systemized dosage schedule with two variables: (a) the size of each drug dose and (b) the time between consecutive dose administrations. Dosage regimen

TABLE 1.1 Therapeutic Concentration Ranges of Some Selected Drugs in Plasma

Drug	Therapeutic usage	Therapeutic concentration range (μg/ml)
Amiodarone	Antiarrhythmic agent	1.0–2.5
Amitriptyline	Tricyclic antidepressant	0.12–0.15
Carbamazepine	Anticonvulsant	4–12
Cyclosporine	Immunosuppressant	0.15–0.40
Digoxin	Cardiac glycoside	0.0006–0.002
Gentamycin	Aminoglycoside antibiotic	4–12
Lidocaine	Local anesthetic and antiarrhythmic drug	1.5–5.0
Nortriptyline	Tricyclic antidepressant	0.05–0.15
Phenobarbitone	Anticonvulsant	15–40
Salicylate	Nonsteroidal anti-inflammatory drug	50–250
Theophylline	Antiasthmatic drug, bronchodilator	10–20
Valproic acid	Anticonvulsant	40–100
Vancomycin	Glycopeptide antibiotic	20–40
Warfarin	Anticoagulant	1–4

calculations are frequently based on population pharmacokinetics and therapeutic drug monitoring.

3. Perform dosage adjustments in patients with, for example, renal and hepatic diseases.
4. Design of dosage form and determination of route of administration, for example, sustained-release versus immediate-release oral dosage forms, and parenteral versus oral dosage forms. The route of administration can affect drug pharmacokinetics.
5. Perform bioequivalence studies, that is, pharmacokinetic evaluations of drug formulations. Some pharmaceutical excipients can enhance or decrease drug bioavailability.
6. Predict drug–drug and drug–food interactions. Both co-administered drugs and various food products can interfere with drug absorption, distribution, metabolism, and excretion.

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