Biopharmaceutics and Clinical Pharmacokinetics

AN INTRODUCTION

Third Edition, Revised and Expanded

Robert E. Notari

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Preface to the First Edition

This book is designed as an introductory text for use in formal courses or for self-study. It is aimed at both biomedical researchers and practitioners. The book assumes no prior knowledge of either kinetics or calculus on the part of the reader. Derivations are provided for those who are mathematically inclined. Those who are not may simply make use of the final or "working" equations. None of the subjects is beyond the level of comprehension of an advanced undergraduate with no calculus background. However, one must approach this book "actively," with graph paper and pencil in hand and with desire to learn well in mind. The material is presented in "building-block" fashion, and it is imperative that the user solve the examples and practice problems to have all of the pieces necessary to build a solid foundation. Topics are covered in a cumulative manner, and skipping a principle will almost certainly result in an inability to understand a subsequent topic fully. Although it is not a programmed text, it must be approached in the same fashion—as a workbook. Casual reading will not suffice.

One problem that faces those who develop an interest in learning biopharmaceutics and pharmacokinetics for the first time is how to get started. Byron once wrote, "Nothing is more difficult than a beginning." This is certainly true for the present subject. Most current references are not written at the basic introductory level. They assume that the reader has some level of sophistication in either calculus or kinetics or both. In addition they do not provide for active participation in the form of problem solving. A teacher wishing to develop a course would have to do so from the literature. Yet it is difficult to read the literature without a fundamental knowledge of the field. This book is meant to provide that knowledge for teachers, students, biomedical practitioners, and research scientists in medicinal chemistry, pharmacology, pharmacy, and other biomedical disciplines. Chapters 2 and 3 comprise the basic introductory materials, and Chapter 4 illustrates some of the applications. An understanding of this text should provide sufficient introduction to the field to allow further reading of more complex applications in the literature.

During the past six years I have been teaching biopharmaceutics to senior students in the College of Pharmacy of The Ohio State University. The absence

of a textbook for the course has presented a number of difficulties. Although assigned readings of review articles and selected chapters have proven helpful, they fail to provide the structural foundation that a textbook achieves. Students repeatedly failed to visualize the total structure of the subject material until the course was nearly complete in spite of the fact that detailed syllabi and other outlines were distributed each quarter. Students were generally accustomed to working with a required text which serves to define the course goals in much more detail and provides a means for reading ahead. Furthermore, when a student experienced difficulties in solving homework problems, there was no reference book to provide additional information over and above that found in the lecture notes. Problem sets had to be created, printed, and distributed in lieu of an available source such as a required text. There was no provision for additional practice problems for the student who felt the need for such experience.

As a result, the outlines, problem sets, graphic demonstrations, classroom handouts, short presentations of principles, etc., grew in both number and in size until some of the materials distributed to the class approached the size of a chapter or even a small book. Most of the contents of this text have evolved from the development of these undergraduate teaching aids. Some of the subject matter was added later to accommodate an intermediate level graduate course. All of the examples and practice problems have been worked many times over by undergraduate and graduate students alike. Over the past two years (and prior to its publication) the book has been successfully used as a required text in both undergraduate and graduate courses here at Ohio State.

It would be impossible to list the names of all those students whose comments and general interest served to stimulate the writing of this book as well as to influence its contents and mode of presentation. Certainly I must acknowledge the graduating classes of the College of Pharmacy of The Ohio State University from 1965 through 1971, who had the dubious honor of serving as "guinea pigs" for the development of this course. Sincere thanks for their patience and enthusiasm. It is with pleasure that I thank the graduate students and faculty who read the text and in some cases helped develop the problems and examples. Among them I wish especially to acknowledge the efforts of Miss Marilyn Lue Chin, Mrs. Joyce DeYoung, Imtiaz Chaudry, Raymond Anderson, and Dr. Richard H. Reuning. The physical appearance of the text is a testimonial to the fine art work of Mrs. Yvonne Holsinger and the excellent typing of Miss Carol J. Lusk.

Finally, any comments, criticisms, suggestions, errors or improvements would be most gratefully received by the author.

Robert E. Notari

Preface to the Second Edition

The objectives of this book are identical to those of the first edition. It is a place to begin your studies—an introduction. Hopefully, it is both simple and accurate. And the agreement between reader and author has also remained constant. This is a workbook. If you are willing to work the problems, the principles should become meaningful to you by the process of discovery.

To that end the second edition has been modified to make it more self-sufficient. As each new principle is introduced, two types of problems are presented. Sample problems are completely solved so that you can diagnose your error when your answer is not correct (and assuming that mine is!). Practice problems are designed to test your ability to apply what you have learned. They are generally slightly more difficult.

The constancy of objectives is not a reflection of a lack of progress in the field or a lack of change between the editions. Indeed, the second edition is largely a new book. In accomplishing the updating and improving of the book, the author gratefully acknowledges the indispensible contributions of co-authors Joyce L. DeYoung (Chapters 2 and 3) and Raymond C. Anderson (Chapter 5).

Those who are familiar with the first edition will find it helpful to know what changes have been made. Chapters 2 and 3 have been completely rewritten and restyled. While they cover the same subject matter, the order of presentation is different. Chapter 2 now contains pharmacokinetic models and the basic kinetics required to understand them. For example, a beaker is still used to teach two-compartment model kinetics, but it is immediately followed by the analogous situation in pharmacokinetics. The basic kinetics are therefore kept minimal and limited to models with pharmacokinetic counterparts. Chapter 3 contains methods and discussions for calculating pharmacokinetic parameters. Among the notable changes is the expansion of the section dealing with the apparent volume of distribution. This has been completely updated to include both discussion and equations regarding variation in calculated values obtained by different methods for multicompartmental drugs.

Chapter 4 has been expanded. It begins with a revised section on the interpretation of blood level curves and ends with a new addition covering

dosage regimen calculations in patients with normal renal function or with renal failure. This latter area is one of the most widely recognized contributions of pharmacokinetic sciences to improved clinical therapy.

Chapter 5 is a new addition to the book. It is aimed at fostering both an understanding and an interest in the effects of molecular manipulation on pharmacokinetic parameters and the resultant pharmacologic impact. This is a field which is relatively undeveloped (as compared with studies on dosage-form effects) but which will be a key to future evaluation and development of new drugs.

The second edition is amply referenced. Each chapter provides sufficient citations for the interested reader to check on the validity or limitations of the subject matter presented or to become more familiar with a particular field.

Again, I would greatly appreciate receiving comments, criticisms, suggestions, opinions, or notifications of errors regarding any section of the book. A similar invitation in the preface to the first edition was accepted by several people, whose comments had a direct influence on the production of the second edition. While I cannot cite them all, I would particularly like to thank Dr. Adam Danek, Dr. Gerald E. Schumacher, Dr. Donald A. Zuck, and Dr. James W. Ayres for their helpful suggestions, encouraging comments, and poignant questions.

Robert E. Notari

Preface to the Third Edition

The first edition, written during the 1960s and published in 1971, noted that "The approaches discussed here may seem a bit too sophisticated and costly to the reader who has not previously come upon the concept of an individualized dosage regimen." This statement followed a discussion suggesting that "pharmacokinetics will make an ever increasing contribution to the rational clinical use of drugs . . ." The second edition (1975) contained "a new addition covering dosage regimen calculations in patients with normal renal function or with renal failure," together with an additional chapter on the pharmacokinetic aspects of molecular modification. The latter was described as "a field which is relatively undeveloped." These applications of pharmacokinetics were minor components in the second edition and absent from the first edition.

The immense progress in these two areas, clinical pharmacokinetics and pharmacokinetic drug design, has necessitated the writing of this third edition. They now occupy roughly one-half of this text. Chapters 5 and 7 are devoted to clinical pharmacokinetics. The application of pharmacokinetics to drug design and evaluation comprises Chapter 6, the longest in the text. Progress in the development of prodrugs represents a major portion of this expanded chapter.

I must reemphasize that the text is not intended as a review but rather an introduction. Development of concepts is the primary goal, and examples have been selected to illustrate them. Problem solving by the reader remains the *modus operandi* for comprehending the principles and their applications. As in previous editions, it is the author's hope that this text will provide a starting place for those who wish to pursue further study or who want only a simplified but quantitative appreciation of the field.

The many inquiries I have received over the years have proven invaluable in identifying areas for revision. I am most grateful to all those who have graciously given helpful comment or asked for clarification; both provide insight that an author cannot attain for himself. I particularly wish to acknowledge Dr. Adam Danek, Dr. Jacek Bojarski, and Dr. Halina Krasowska, who stimulated the publication of the second edition in Poland (1978) and who translated the English edition into Polish. This experience provided great encouragement to me, and the questions surrounding the translation called attention to several

ambiguities that have led to rewording in the third edition. The continued beautiful art work of Yvonne Holsinger and the excellent typing of Sue Sheffield are most sincerely appreciated.

I would be grateful to receive any comments or questions from readers of the third edition as I truly regard both as a service to the author.

Robert E. Notari

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Chapter 1

BIOAVAILABILITY

It is both an enlightening and astonishing experience to read the labels on so-called cure-alls and tonics on display in museums and occasionally found collecting dust in remote corners of storerooms in old established pharmacies. Since we are no longer obliged to take these medicines when we become ill, we may even see a great deal of humor in their claims. Therapeutic effectiveness was generally certified on the basis of testimonials or anecdotal evidence. Modesty was not a characteristic of promotional statements. *Hamlin's Wizard Oil,* "The Great Medical Wonder," recognized no limitations in stating "There is no sore it will not heal. No pain it will not subdue." *Dr. King's New Discovery* was favorably compared with other recent inventions such as the steamship, steam engine, automobile, telephone, telegraph, and radio. According to the advertisement it rated well as "The Greatest of All." "*No-To-Bac* made a man of me," another advertisement read, and picturing a young man embracing a young woman it noted that by use of this product he had "thrown away his pipe and tobacco and thereby won the love of this stunning girl." A delightful review of that era can be found in the book, *One for a Man, Two for a Horse* [1]. That title in itself shows that individualization of dosage regimens (discussed in Chap. 5 of this text) is not as innovative as one might think. As a final example of immodest claims and an unbelievable dosage regimen, consider the statement regarding *Pond's Extract* and made by the popular fictional character, Buster Brown: "From my own personal experiences, *Pond's Extract* is the best remedy for all inflammations, hemorrhages, sprains, cuts, bruises, chill blains, burns, scalds, frostbite." So much for the indications. Now for the clinical results: "It has made a better and healthier boy of me and is my best friend." And finally the dosage regimen: "Used externally, internally, and *eternally.*"

How well did the products and claims of yesteryear measure up to the standards of today? One might use the following criteria:

1. Contents
2. Percent strength

3. Purity
4. Safety
*5. Clinical effectiveness
*6. Bioavailability

Not only did the contents of such products not appear on the label, but it is unlikely that the manufacturer himself knew the ingredients. If the contents are not known, the question of percent strength becomes meaningless. Plant sources sold for the production of drug products were often adulterated. Even if the plants used were pure, the active ingredients, if there were any, were not known. Chemical analyses were neither possible nor of great concern to a naive society. Some awareness of the danger in such a system probably evolved as a direct result of unfortunate experiences with products that not only failed to cure but also caused toxic effects that may have been worse than the malady. Initially, society responded with legislation aimed at ensuring that medicines were safe and free from adulterants. No doubt these seemingly simple goals presented tremendous problems, without adding concern for therapeutic effectiveness which was generally certified on the basis of testimonials or anecdotal evidence.

The development of analytical chemistry brought about an acute awareness of the importance of controlling the contents of a product. That each drug should have an adequate purity rubric became the concern of those given the responsibility for setting standards for the protection of society. Tests for physical characteristics were introduced, and as analytical technology advanced the sophistication of product tests increased. Trace analysis made limitations on allowable contamination practical. Chemical content and product purity advanced to a scientific level commensurate with the analytical technology of the day.

And so we can observe that since the turn of the century, product development has evolved from cure-all herb teas to stable, pure formations containing known amounts of chemicals that have been defined as drugs. It was quite natural that the scientific community and society at large had confidence in a product which adhered to its purity rubric. This philosophy dominated from 1938 (when the final drug safety amendments to the Federal Food, Drug, and Cosmetic Act were made) until relatively recent years. During that time it was widely assumed that all products containing equal doses of the same drug were equipotent when put to use by the clinician. The first four criteria in our list were regarded as sufficient. More recently, we have come to the sometimes surprising realization that percentage chemical strength is not the sole criterion for clinical effectiveness. In fact, formulations were produced and marketed which satisfied all of the required legal standards but were not therapeutically active. It became obvious that a dosage form must not only contain the correct amount of the labeled drug but must also release that drug upon administration to the patient. *Clinical effectiveness* and *bioavailability* were thus added to the

criteria for effective drug product development. A drug should be not only safe, but beneficial as well, and its therapeutic claims must be based upon sound clinical evidence. Furthermore, a drug which has been proven effective can be rendered ineffective due to lack of bioavailability.

What is bioavailability? The simplest concept to consider is that of a *bioavailable dose.* This is the dose available to the patient, in contrast to the dose stated on the label. Only a drug that is completely absorbed into the bloodstream will have a bioavailable dose equal to that stated on the label. In the case of tablets or capsules administered orally, the bioavailable dose will generally be less than the administered dose. Bioavailability therefore deals with the transfer of drug from the site of administration into the body itself as evidenced by its appearance in the general circulation. Since a transfer process is involved, it may be characterized by both the rate of transfer and the total amount transferred. The bioavailable dose refers only to the total amount transferred. A complete description of the bioavailability of a drug from a dosage form must include both the rate and the amount. Methods for such characterizations are discussed in this book. Bioavailability has been defined in various ways [2-5]. Those which ignore the rate of transfer [2,3] are inadequate to explain cases where products show differences in blood levels and/or clinical response due in total or in part to rate of release of drug. A more acceptable definition for *bioavailability* is therefore [5]: "A term used to indicate the rate and relative amount of the administered drug which reaches the general circulation intact."

The measure of success in the use of any drug is the degree to which the results obtained agree with those expected. Therefore, the degree of success achieved by the use of a drug product may be altered by factors which affect bioavailability, such as certain foods, other drugs, the dosage regimen, the route of administration, a less than optimum formulation, or the inappropriate use of a suitable formulation. Biopharmaceutics deals with such problems. It is concerned with obtaining the expected therapeutic effect from a drug product when it is in use by the patient. One such definition has been offered as follows [5]: "*Biopharmaceutics* is the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacologic or therapeutic activity of drug products in clinical application."

Since studies involving the rates of drug transfer employ kinetic methods, biopharmaceutics is closely linked to pharmacokinetics. Indeed, the terms have been interchanged often in the literature. In this book the following definition [5] will be used: "*Pharmacokinetics* is the study of the kinetics of absorption, distribution, metabolism, and excretion of drugs and their pharmacologic, therapeutic, or toxic response in animals and man."

Finally, consider the term *bioequivalency.* Like the others, it has been defined in various ways. We shall use the simplest interpretation. Two drug products containing equal doses of a drug will be said to be bioequivalent if they do not differ significantly in either their bioavailable dose or its rate of supply.

Thus, the time course for drug in the blood following administration of either product would be identical. Bioequivalency therefore includes not only the amount of active ingredient available but also the rate at which it is available.

A corollary to the more recent concerns for product quality and effectiveness is the challenge to physicians and pharmacists to consider the impact of these sciences on clinical practice. For example, the clinician must be informed when the co-administration of other drugs or foods may influence the bioavailability of an active ingredient. As research defines the critical factors influencing the absorption of drugs, the information must be put to clinical use so that practitioners are aware of those situations that should be avoided.

This concept can be further extended into all areas of biomedical drug research. Let us consider pharmacology as a case in point. In a broader sense the concept of bioavailability cannot be circumvented by choice of route of administration. Regardless of where the experiment begins, the final observations are a function of the bioavailability of the drug to the site of action, and the factors influencing its arrival there are many. Since the movement of drug from the site of administration to the site of action requires time, the overall process may best be analyzed by pharmacokinetics. Thus, the bioavailability time profile is again critical in the comparison of drugs or drug analogs. A pharmacological study is greatly enhanced by a knowledge of how much of the drug has reached the receptor as a function of time.

The concept of bioavailability in biomedical drug research, pharmaceutical product development, and rational clinical use of formulations is the subject of this book.

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Chapter 2

RATE PROCESSES IN BIOLOGICAL SYSTEMS

I. INTRODUCTION

After a drug is introduced into a biological system it is subject to a number of processes whose rates control the concentration of drug in the elusive region known as the "site of action," thus affecting its onset, its duration of action, and the intensity of the biological response. Some knowledge of these rate processes governing the fate of a drug is therefore necessary for a full understanding of the observed pharmacological activity of the drug.

While presupposing no formal background in kinetics, pharmacokinetics, or calculus, this chapter is designed to teach the basic principles of compartmental modeling. A limited number of simple derivations are included in the text, but it is possible to make use of the results without having the mathematical skill to carry out the derivations. For those who have some proficiency in calculus there are a few more advanced derivations and brief discussions regarding their significance in the Appendix.

In assuming minimal experience on the part of the reader, the chapter presents the subject using a "self-study" approach. Each topic is followed by a sample problem for which a method of solution is provided. A practice problem covering the same principles but including only the final answers follows each sample. Solutions to the samples and practice problems may appear obvious, but the experience acquired by working them through is prerequisite to a complete comprehension of the subject matter. You will need semilog paper (2 cycles × 10 to the inch and 1 cycle × 60 divisions) and coordinate paper (20 squares to the inch). A natural log table is included at the end of this book.

II. TRANSPORT OF DRUGS

A. Passive Diffusion

1. Two-Compartment Closed Model

Consider the case where both compartments in Fig. 1 contain equal volumes of water. Both compartments are therefore equivalent in all respects. Let us dissolve some drug in the water contained in compartment A. Since the barrier is permeable to drug, we would expect drug molecules to pass freely from compartment A to compartment B and vice versa. However, there will be a net