Biopharmaceutics and Drug Interactions

Donald E. Cadwallader, Ph.D.

THIRD EDITION

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Preface

Members of health care teams have become increasingly aware of the importance of publications in the fields of biopharmaceutics and drug interactions. This has become very pleasantly clear from the great demand by pharmacists, physicians, nurses, educators, and students for previous editions of this book. It is apparent that health care professionals want to keep up-to-date on current pharmaceutical and medical problems, and to acquaint themselves with new concepts, procedures, and evolving subject areas pertinent to their profession.

Rapid developments in the fascinating and expanding areas of biopharmaceutics and drug interactions have led to the publication of this third edition. Sections on bioavailability testing and drug product selection have been expanded, and many new figures and tables—published recently in the scientific literature—have been added. Full citations of the original literature are presented under the figures and tables so that the reader can acquire an appreciation of the scientific work being carried out and become knowledgeable of the primary scientific literature dealing with biopharmaceutic and drug interaction phenomena.

Any member of the health care team possesses the ability and background to understand and absorb the subject material presented in this text on the basis of his academic training in the biological and physical sciences and the associated pharmaceutical and medical sciences. The areas of biopharmaceutics and drug interactions utilize and correlate all these disciplines in a manner relevant to the contemporary practice of pharmacy and medicine. The illustrations, whenever possible, relate directly to drugs and drug products familiar to the practitioner in his daily routine.

This volume is designed for the practitioner who does not have the time to master these subjects through a formal curriculum, but who wants access to information on current pharmacy and medicine. For students in any of the health care professions the book can serve as a primer on biopharmaceutics and drug interactions. My hope is that the reader will be encouraged to gain greater insight into biopharmaceutics and drug interactions by utilizing the references in the selected reading list given at the end of this book, by enrolling in independent study courses, and by attending seminars and continuing education courses on these subjects.

Donald E. Cadwallader

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Introduction

To understand the underlying principles of biopharmaceutics and the basic principles of drug interactions, it is necessary to understand the fundamentals of drug absorption, transport (distribution), metabolism (biotransformation), and excretion. This is the common ground for discussing and correlating biopharmaceutical phenomena and drug interactions. The purpose of the discussions in this book is to develop this understanding.

Presentation of the subject material is as follows:

1. The fundamentals of a specific phenomenon, e.g., absorption and drug absorption
2. A discussion with illustrations on the biopharmaceutical relationships pertaining to the specific phenomenon, e.g., the influence of formulation on the absorption of drugs
3. Drug interactions that might or do occur with relation to the specific site, e.g., drug interactions in the gut and gut wall

The same type of format is used for transport, metabolism, and excretion phenomena. Mathematical equations have been kept to a minimum and when used are strategically placed in the text so that the reader has a clear idea of the practical applications of the subject matter before analyzing the equations.

Biopharmaceutics

You can hardly pick up a professional journal or newsletter today, or for that matter a magazine or newspaper, without reading something about generic equivalency, therapeutic efficacy, drug availability, drug substitution, or drug product selection. All these topics are part of a field of pharmacy called biopharmaceutics. The concept of biopharmaceutics has arisen out of a combination of disciplines. When drug product development research became highly active during the last 15 to 20 years, it was recognized that a great deal of background knowledge is required for studying the many factors that affect the biological activity of administered medication. It was realized that dosage form design, for example, must, in the final analysis, take these factors into account.

The term "biopharmaceutics" and a definition of it first appeared in print in a review article by Wagner in 1961 (4):

> Biopharmaceutics encompasses the study of the relation between the nature and intensity of the biological effects observed in animals and man and the following factors: *(a)* simple chemical modification of drugs such as formation of esters, salts, and complexes; *(b)* modification of the physical state, particle size and/or surface area of the drug available to the absorption sites; *(c)* presence or absence of adjuvants in the dosage form with the drug; *(d)* the type of dosage form in which the drug is administered; and *(e)* the pharmaceutical process or processes by which the dosage form is manufactured.

Therefore, biopharmaceutics may be defined as the study of the influence of formulation on the therapeutic activity of a drug product or of the relationships between some of the physical and chemical properties of the drug and its dosage forms and the biological effects observed following its administration in its various dosage forms. Biopharmaceutics includes: (a) all possible effects observed following the administration of the drug in its various dosage forms; (b) all possible effects of dosage forms on biological response; (c) all possible physiological factors which may affect the drug contained in the dosage form; and (d) the dosage form of the drug itself. To prevent possible confusion with other rapidly growing and closely related fields, biopharmaceutics is best defined as *the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacological or therapeutic activity of drug products in clinical application.*

The biological availability of a drug may be greatly affected by its physical state and by the dosage form in which it is administered. A given drug may show different degrees of availability from one dosage form to another when given by the same route. For example, a drug might have different onsets of action or show different blood level concentrations depending on whether it is administered as a tablet, capsule, or suspension. Also, a given drug might show different availability from the same dosage form depending on the manufacturer; there is also the possibility of different availability from one lot of the drug to another, even when made by one manufacturer.

There are many and varied pharmaceutical factors that may alter drug availability. Some of the physicochemical factors are:

1. The particle size of the drug in solid dosage form. Some drugs, e.g., griseofulvin, are made available as the microionized form to increase their low dissolution rate. Inadequate particle size was one cause of the relatively

poor availability of several generic chloramphenicol capsules which were recalled several years ago.

2. Particle size of the dispersed phase in an emulsion.

3. Tablet disintegration. This may depend not only on the type and quality of the disintegrating agent but also on the hardness of the tablet.

4. Tablet and capsule adjuncts. Diluents, binders, and lubricants, for example, may decrease water permeability and consequently reduce drug absorption.

5. Tablet coatings. Some of these may release drugs unevenly or not at all.

6. Crystalline drug properties. The crystalline, or amorphous, form of the drug may have a profound effect on the dissolution rate of the drug after ingestion. Cortisone acetate and novobiocin are examples of drugs whose availabilities are altered by changes in their crystalline forms.

The physicochemical properties of a compound are measurable characteristics by which the compound may interact with other systems. The physical and chemical properties of a molecule are determined by the number, kind, and arrangement of the atoms. Both properties are closely interrelated, and for this reason the term "physicochemical" is the preferred expression of the properties that relate to biological action rather than either physical properties or chemical properties used singly. Some examples of physicochemical properties are solubility, pH, surface activity, hydrogen binding, and partition coefficients.

In addition to physicochemical factors, of course, drug availability is affected by various pharmacological, physiological, and biochemical factors.

Although the field of biopharmaceutics has grown rapidly during the last decade, it has only been in recent years that subject material pertaining to biopharmaceutics has been incorporated into the undergraduate pharmacy curriculum. Therefore many practicing pharmacists have never been introduced to this new and important area of pharmacy. The individual pharmacist has the responsibility of understanding biopharmaceutics. He should be able to discuss with physicians, nurses, and other professionals the effects of dosage forms on the therapeutic efficacy of a drug. The pharmacist should understand why two drug products may be different and should be able to make informed drug product selections for his patients.

Drug Interactions

Drug interaction is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another (or the same) drug(s). It occurs, more specifically, when the overall biological

response to the simultaneous (or nearly so) administration of two or more drugs is markedly different from the simple sum of the effect of each compound given singly. During the last several years there has been an increasing awareness of drug interactions, e.g., when one drug alters the expected therapeutic response of another drug that has been administered just prior to, simultaneously with, or just after another drug. Interest in adverse drug reactions and drug–drug interactions is currently enormous and is growing every day.

Drug interactions present a complex and profound problem. They may arise either from *alteration of the absorption, distribution, biotransformation, or excretion* of one drug by another, or from a combination of their actions or effects. With newer and more sophisticated and potent drugs, and with the proliferation of drug therapy, the problem can only get worse! Understanding the basic mechanisms by which drug interactions occur will help the members of the health team to anticipate possible drug–drug interactions. This situation gives the pharmacist an opportunity to utilize his education and training for the benefit of the patient. Knowledge of drug actions, reactions, and interactions, and communicating this information to other members of the health team, are among the most important functions of the pharmacist.

If, as one study has shown (1), the patients in our hospitals receive an average of 14 medications during their hospital stay, what are the chances that one of these drugs will affect the subject's reactivity to another drug?

Although outpatients usually take fewer medications than hospitalized patients, the risk of a drug interaction in today's world is increased by several factors:

1. The practice of polypharmacy is alive and well today. When a patient sees a physician he may expect more than one medication for an ailment. The tradition of prescribing a combination of drugs is still common. Indeed it is difficult to adequately treat many ailments with a single medication.

2. In this age of specialization, many patients see more than one physician concurrently, none of whom may be aware of the others' involvement with the patient and his drug therapy.

3. Self-medication is prevalent, and multiple-drug use is practiced by individuals who take numerous over-the-counter (OTC) medications for various ailments.

4. Many drugs used today are very potent and are given in doses that are close to their toxic level (the therapeutic index of the drug is low). Also many drugs have powerful side effects.

5. Many modern drugs are polymechanistic and may affect several or many physiological and biochemical systems of the body.

In an interesting and realistic presentation, Knyvett of the Royal Brisbane Hospital, Australia (2), pointed out that this is the era of symptomatic therapy in medicine. From the enormous amount of prescribing by physicians and self-medication by patients, it is apparent that many people seem to have a psychological need to take something for every ailment, real or imagined. If a person has a common cold, he may take some aspirin, drink plenty of fluids, and retire to bed. This is a good treatment, but how many people would be happy to pay the doctor for the same advice? Experiences indicate that if patients were treated at the physician's office or clinic, or in a hospital, they would get some or all of the drugs appearing in Table 1-1. This regimen is quite different from the self-medication therapy; however, each of these preparations has symptomatic value. Each can be justified, and in many cases several combinations might be essential to the proper management of the patient. On the other hand, each may on some occasions produce side effects, and many, if given concurrently, may give rise to drug interactions.

Of special concern to the medical community is the high potential for drug interactions in the elderly. As people grow older, they demonstrate a need for multiple-drug therapy to treat a variety of disease states. The ingestion of numerous drugs coupled with the possible decrease in physiological capabilities make the elderly particularly susceptible to adverse drug reactions and drug–drug interactions. Age is an important physiological factor in the consideration of drug reactions and interactions. Studies indicate that there is an increased incidence of adverse drug reactions in geriatric patients, and an estimate by Melmon (3) suggests that the risk of drug

TABLE 1-1. *Treatment of common cold*

Possible self-treatment
Aspirin
Hot or cold drinks
Perhaps some favorite alcoholic beverage
Bed rest
Possible physican treatment after visit
Compound codeine tablets—for aches and pains
Nose drops—to free the nasal airway
An antihistamine—to reduce nasal "allergic" congestion
An inhalant—to reduce nasal congestion
An antitussive syrup—to ease a cough, present or anticipated
Often an antibiotic—to "prevent" secondary infection
Sleeping pills—to ensure some restful nights
Sometimes a laxative—prescribed by the doctor who is aware of the constipating effects of codeine and fever

Adapted from Knyvett, A. F. (1968): The hazards of drug therapy. *Austral. J. Pharm.*, 49:394.

reaction in patients 60 to 70 years old is almost double that in adults 30 to 40 years old. Although renal and hepatic function in the elderly may be diminished, there is no evidence that these factors in general are responsible for the high incidence and severity of drug reactions and interactions in the elderly. The aging process leads to many disease states—some acute, some chronic—and one disease state may lead to another. This theme is developed in Fig. 1-1. Diabetes, arthritis and bursitis, glaucoma, emphysema, ulcers, and other gastrointestinal (GI) disorders, urinary tract problems, high blood pressure, atherosclerosis, heart failure, and stroke are only some of the diseases associated with advanced years. It is a fortunate senior citizen who suffers only one or two of these conditions. In addition to this, the eyes of the elderly are getting weak, hearing is failing, and constipation is becoming a way of life. Figure 1–1 shows that multiple diseases—in fact many single diseases (high blood pressure, for example)—lead to multiple-drug therapy; and the more drugs a patient takes into the body, the greater are the chances of adverse reactions and interactions. The geriatric patient, because of a general debilitated condition will likely have a stronger reaction or interaction to drug therapy than a younger adult.

Dispensers of drugs should be aware of the potential for lawsuits associated with harm to a patient from a drug interaction. There is growing recognition by the courts that detection of adverse drug interactions during the dispensing of medication is the responsibility of the pharmacist, and proper procedures should be utilized to monitor patients' prescriptions. Maintenance of patient medication records to assist in detecting potentially dangerous drug interactions is an increasing service provided by pharmacists. Some states mandate that patient profiles be maintained.

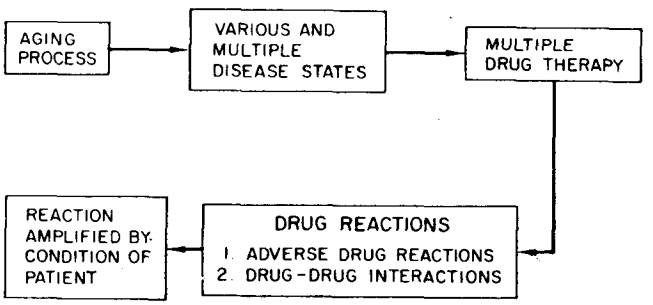

FIG. 1-1. Multiple-drug use and adverse reactions in the aged. [From Cadwallader, D. E. (1979): Drug interactions in the elderly. In: *Drugs and the Elderly—Social and Pharmacological Issues*, edited by D. M. Peterson, F. J. Whittington, and B. P. Payne, p. 81. Charles C Thomas, Springfield, IL.]

One must view drug interactions in the proper perspective. Many interactions apparently are clinically insignificant to the majority of patients. Also, to deny a patient needed therapy might not be warranted because of a possible interaction. In fact, most combinations of drugs can be safely used provided the patient is carefully counseled and monitored. Nevertheless, the physician must be informed of a potential hazard and the pharmacist should be a prime source of this information.

Drug interactions have been known for years to be a beneficial aspect of drug therapy as well as a danger. For example, the concomitant administration of probenecid (Benemid®) with penicillin products is a widely used practice for maintaining high antibiotic blood levels. Most antidote therapy for drug overdose involves nullifying the toxic drug by interaction with another drug.

The potential hazards, and the ones we need to be aware of, are those unwanted or unsuspected interactions that may cause harm to the patient. The main emphasis in this book is placed on drug interactions that result from interactions with other drugs (drug–drug interactions). Some of the important hazards that result from interactions with components of the diet, e.g., milk and tetracyclines, monoamine oxidase inhibitors (MAOI) and tyramine in aged cheese, are discussed. Possible interactions with environmental components such as cigarette smoke and some interactions with endogenous physiological chemical agents are also presented. In all these discussions a drug is "any biologically active substance," a widely accepted definition.

The means by which drug interactions occur, when they do, are varied and complex, including:

1. Action—chemical or physical—of one compound directly on another
2. Modification of GI absorption
3. Competition for protein-binding sites during transport
4. Modification of a drug's action at a receptor site
5. Acceleration or retardation of the metabolism of a given drug by modification of enzyme systems
6. Modification of the rate of urinary excretion-renal clearance.

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2

The Complex System

Whenever biopharmaceutics and drug interactions are discussed, there is always reference to systems and events or sequences of events that are very complex. The pathways and sequence of events for drug disposition can be represented by various schemes and diagrams. Drug disposition is a term used to describe the simultaneous effects of distribution and elimination. To exert their biological effect, drugs must be soluble in and transported by body fluids, pass membrane barriers, escape excessive distribution into inert body depots (where they cannot act), endure metabolic attack, penetrate to their sites of action, and act so as to cause an alteration of a particular function—termed the *action* of a drug. This action, or biological response to a drug, is a consequence of the interaction of that drug with the living system, causing some change in the biological state that was present before the drug was administered.

Figures 2-1 and 2-2 illustrate the complexity and the great amount of interplay that takes place between absorption, transport, metabolism, and excretion. When a drug is administered orally, it first must be dissolved in the GI fluids before transport can take place across a membrane into the systemic circulation. The drug is then distributed to various parts of the body where it may be stored, metabolized, exert a pharmacological action, or be excreted. As drugs may be distributed indiscriminately to all parts of the body, they sometimes exert actions that are not needed and therefore in many instances cause undesirable side effects.

The transfer of drug from the site of administration (e.g., GI tract or intramuscular injection site) to the bloodstream is called *absorption*. The absorption process can be greatly influenced by formulation factors. *Distribution* is associated with the transfer of drug from the circulating blood to other parts, or compartments, of the body (e.g., lymph fluid, muscle tissue, liver, kidneys). *Metabolism*, or biotransformation, of drugs takes place in the liver and other parts of the body. The main site of *excretion* for most drugs is the kidney. The term *elimination* refers to the combined effects of metabolism and excretion.

Arrows are used in the diagrams in this book to indicate direction of flow or transport of the drug. In many cases arrows go in both directions across membranes, and in some instances they indicate that cyclic processes are taking place, e.g., the recycling of drug back to the small intestine via the bile fluid, with its subsequent reabsorption. The Ks above the arrows indicate rates of absorption, transport, metabolism, and excretion, these rates being different for different drugs and membranes and for different conditions of the system. The purpose of the science of *pharmacokinetics* is to study the time course (rates, or Ks) of drug and metabolite concentrations and amounts in various tissues and excreta, and to construct models to interpret such

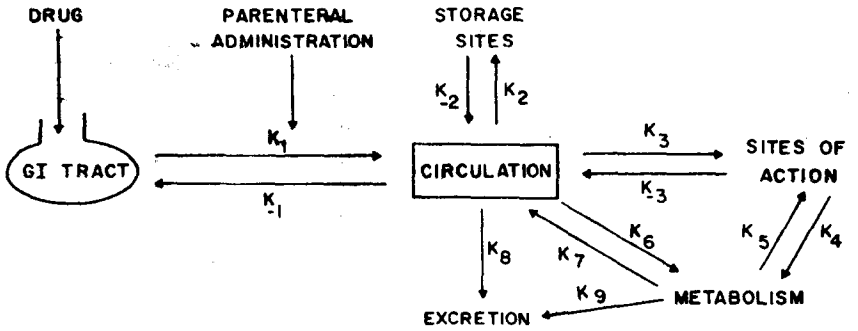

FIG. 2-1. Complex of events between drug administration and action

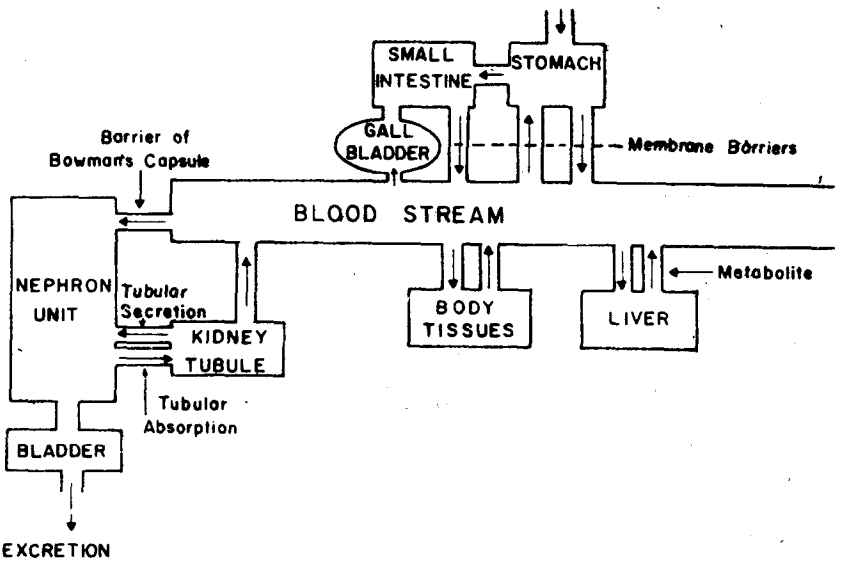

FIG. 2-2. Absorption, transport, metabolism, and excretion. [Adapted from Stuart, D. M. (1968): Drug metabolism—Part II. PharmIndex, 10:5.]

data. Pharmacokinetics is mainly concerned with the kinetics, or dynamics, of absorption, distribution, metabolism, and excretion of drugs and some endogenous substances; it includes the relationship between pharmacological response and concentrations of drugs or their metabolites in body fluids. A function of pharmacokinetics is to describe what the body does to a drug. The application of pharmacokinetics to establishing the optimum dose size and dosing intervals for an individual patient is of growing interest to the medical care team.

The fact that only a fraction of the original dose of drug taken orally may reach the systemic circulation is shown in Fig. 2-3. There are many factors that can influence the amount of drug that reaches the systemic circulation. As soon as a drug is ingested, it enters a hostile environment, where it may be destroyed by chemical and enzymatic action, be incompletely absorbed, be bound and inactivated in tissues, or be metabolized in various body compartments. The drug that finally reaches the systemic circulation is now subjected to additional binding, biotransformation, and excretion before a

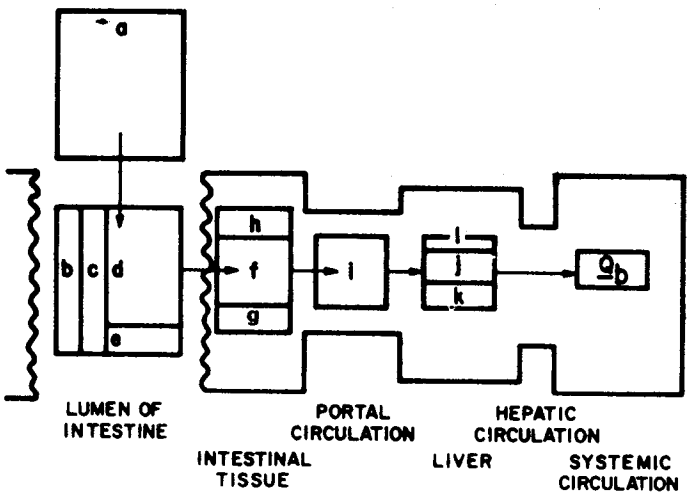

FIG. 2-3. Some factors that influence the amount of drug reaching the systemic circulation. **a** = Total drug in dosage form. **b** = Drug degraded in GI fluids (e.g., acid-catalyzed hydrolysis). **c** = Drug metabolized by GI enzymes (e.g., esterases). **d** = Drug in solution which is abosrbed. **e** = Drug in solution which is not absorbed. **f** = Drug in intestinal mucosa which is transferred to the portal circulation. **g** = Drug in mucosal cell which is metabolized (e.g., glucuronide) which may pass into the lumen or the portal circulation. **h** = Drug bound in intestine (e.g., iron). **i** = Drug in portal circulation. **j** = Drug first in liver then transferred to the body. **k** = Drug in liver where it is metabolized. **l** = Drug bound in liver. Q_b = Amount of drug which finally reaches the body. [From Barr, W. H. (1968): Principles of biopharmaceutics. *Am. J. Pharm. Educ.*, 32:958.]