Bioavailability of Parenteral Drugs I. Intravenous and Intramuscular Doses

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Introduction

It has long been recognized that the intensity and duration of pharmacologic effect of a systemically acting drug are functions, not only of the intrinsic activity of the drug, but also of its absorption, distribution, and elimination characteristics.

To exert a required pharmacological action, a drug must be absorbed at a rate and to an extent that will produce adequate drug concentrations at the site(s) of action during a certain time period. The relationship between drug concentration at the receptor site and pharmacological effect depends also on the type of action the drug exerts.

For example, present knowledge suggests that the bacteriocidal action of antibiotics is directly related to the drug levels at the site of the infection, and the bacteriocidal effect is lost when antibiotic levels fall below the minimum inhibitory concentration of the invading organisms. On the other hand, the effect of the anticoagulant warfarin on blood clotting is considerably delayed relative to the circulating drug profile, and the relationship between circulating levels of this compound and its therapeutic effect is less well defined.

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Whatever the mode of action of a systemically acting drug, the efficiency and also the rate of its absorption into the circulation are of primary importance. During the last 10 years there has been a proliferation of literature related to the biological availability, or bioavailability, of systemically acting compounds. The impetus for this has derived firstly from a growing awareness among clinicians and biological scientists of a relationship between drug bioavailability and therapeutic effect, and secondly, from the recent increase in the number of multiple-source drug products and also the expiration of patents on many proprietary drug formulations. The combined effect of these perhaps diverse interests has been to generate a vast amount of data, and also rhetoric, on drug bioavailability and its importance in therapy.

The term bioavailability has been defined in the United States Federal Register (1) as "the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of action"—normally estimated by its concentrations in body fluids, rate of excretion, or acute pharmacological effect.

Although a number of methods involving the use of pharmacological response have been described for measuring drug bioavailability, the majority of studies is based on the chemi-

cal determination of drug or metabolites in biological fluids.

While the bioavailability of drugs administered via the oral or enteral route has been investigated to a great extent, few studies have attempted to address the bioavailability problems associated with drugs which are dosed parenterally. Drugs given by parenteral routes are not subject to enzyme degradation in the gastrointestinal tract or to hepatic metabolism during their "first-pass" through the hepato-portal system. Nevertheless, with the possible exception of intravenous doses, drug absorption from parenteral administration is often incomplete, and bioavailability considerations therefore are necessary.

This review addresses the problem of the systemic availability of drugs which are administered by parenteral routes. The review is divided into two parts. The first considers drug pharmacokinetics and bioavailability in general, and also drug bioavailability from intravenous and intramuscular doses in particular. The second part considers drug bioavailability from other parenteral dosage routes.

Basic Pharmacokinetic Concepts Governing Drug Levels in Blood

Drug Absorption

In all except the intravascular routes of administration, the drug must be absorbed in order to enter the systemic circulation. A prerequisite of absorption is that the drug be released from the dosage form. Drug release depends on the physical and chemical properties of the drug, the dosage form, and also the body environment at the site of administration.

When a drug solution is administered, or following the dissolution of a solid dosage form, drug molecules diffuse into the circulation by crossing one or more biological membranes. Theories regarding the basic structure of biological membranes are constantly changing, and one of the most recent and generally acceptable concepts which has been proposed by Singer and Nicolson (2) is shown in Figure 1. In this model the basic

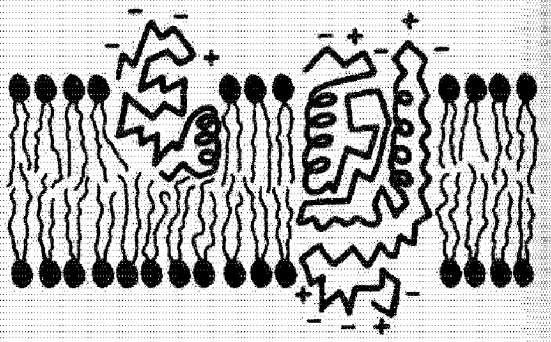

Figure 1—The lipid-globular protein mosaic model of membrane structure: schematic cross-sectional view. The phospholipids are depicted as a discontinuous bilayer with their polar heads oriented outward. The integral proteins are shown as globular molecules partially embedded in and protruding from the membrane. Reproduced, by permission, from Science *175, 720–731 (1972).*

structure is a discontinuous bilayer of phospholipids, oriented so that their polar heads are in contact with the external aqueous environment. Associated with the lipid bilayer are globular proteins, which are embedded into and protrude from the bilayer, in some cases passing from one side of the bilayer to the other. The charged portion of the protein protrudes from the membrane surface while the uncharged portion is embedded within the lipoidal portion of the membrane. Although there are other theories regarding membrane structure, the model proposed by Singer and Nicholson appears to be consistent with the relative membrane penetration characteristics of lipophilic and hydrophilic molecules.

The mechanisms of drug absorption include passive diffusion and specialized transport processes, the former being far more common. In the case of passive diffusion, the drug in aqueous solution at the absorption site dissolves in the lipid material of the membrane, and passes through the membrane to reach an aqueous environment on the other side. Thus, effective absorption is favored when a drug molecule has both lipophilic and hydrophilic properties. Most drugs are organic weak electrolytes, whose ionized forms are soluble in water but almost insoluble in lipids, while the unionized forms have the converse solubilities (3). Therefore, the pKa of the drug and

TABLE I. pKa Values of Some Medicinal Acids and Bases Which May be Administered Parenterally (4)

Acid	pKa	Base	pKa
Acetazolamide	7.2	Adriamycin	8.2
Carbenicillin	2.6	Aminophylline	5.0
Cefazolin	2.1	Chlordiazepoxide	4.8
Cephaloridine	3.4	Cimetidine	6.8
Cephalothin	3.6	Codeine	8.2
Diazoxide	8.5	Diazepam	3.4
Fluorouracil	8.0, 13.0	Dipyridamole	6.4
Furosemide	3.9	Erythromycin	8.8
Methicillin	3.0	Gentamicin	8.2
Moxalactam	2.5	Metoprolol	9.7
Nafcillin	2.7	Pentazocine	8.8
Phenobarbital	7.4	Procainamide	9.2
Phenytoin	8.3	Propranolol	9.5
Sulfisoxazole	5.0	Trifluoperazine	8.1
Thiopental	7.5	Vinblastine	5.4, 7.4

the pH at the absorption site will determine the extent of drug being unionized and absorbable. The pKa values of some acidic and basic drugs, which may be administered parenterally, are listed in Table I (4) while nominal pH values of some body fluids and sites are given in Table II. Acidic compounds are predominantly in the unionized form at pH values below their pKa while basic compounds are predominantly unionized at pH values above their pKa, so that comparison of the data in Tables I and II will give an indication of the fraction of drug which is in the unionized, lipophilic form at various sites. The percentage of drug which is unionized, the lipophilicity of the unionized species, and also the adsorption of drug to the membrane surface, are principal factors governing drug-membrane penetration.

TABLE II. Nominal pH Values of Some Body Tissues and Fluids (4)

Site	pH
Blood, arterial	7.4
Blood, venous	7.39
Blood, maternal umbilical	7.25
Cerebrospinal fluid	7.35
Milk, breast	7.0
Muscle, skeletal	6.0
Prostatic fluid	6.5
Saliva	6.4
Sweat	5.4
Urine	5.8

The rate of passive diffusion of drug through the lipid membrane depends on the concentration gradient across the membrane. Based on Fick's first law, the flow across an area A per unit time is proportional to the concentration gradient, dC/dx, such that:

$$\text{Flow} = -D \cdot A \cdot dC/dx \qquad \text{(Eq. 1)}$$

where D is the diffusion coefficient, and the negative sign indicates that flow occurs down a negative concentration gradient.

Equation 1 can be written as:

$$\text{Flow} = -D \cdot A \cdot (C_{\text{outside}} - C_{\text{inside}})/h \qquad \text{(Eq. 2)}$$

where the C symbols represent drug concentrations on either side of the membrane and h is the membrane thickness. If one assumes that drug is carried away from the membrane by the surrounding fluids as soon as it has crossed, then $C_{\text{outside}} \gg C_{\text{inside}}$ and Eq. 2 can be written as:

$$\text{Flow} = -kC_{\text{outside}} \qquad \text{(Eq. 3)}$$

in which D, A, and h have been combined into a new first-order permeation constant k. In general, absorption and membrane penetration of drugs can be described by a simple first-order expression of the form of Eq. 3.

Drug Distribution

A drug entering the systemic circulation rapidly distributes throughout the blood or plasma. The drug leaves the circulation via the capillary walls, and passes into other body fluids and tissues, depending on its lipophilicity, the permeability of tissue membranes, the affinity of drug to particular tissues and fluids, and on the rate at which blood is supplied to the tissues.

The extent to which a drug distributes throughout the body is often described (frequently incorrectly) in terms of its apparent volume of distribution, V, which may be obtained by expressions of the form:

$$V = \frac{\text{Amount of drug in the body}}{\text{Concentration of drug in plasma}} \qquad \text{(Eq. 4)}$$

Another important property influencing the distribution characteristics of a drug is its binding to plasma proteins, primarily albumin. Plasma protein binding is reversible, and the percent of dose bound is dependent on the nature of the drug molecule, the capacity of the protein, and the concentration of total drug in plasma. The drug which is bound to plasma proteins at any time cannot cross the capillary walls, and is not free to distribute into body tissues. Therefore, for a drug which is extensively plasma protein bound, the plasma concentration of total drug will be unduly high compared to free drug in extravascular fluids, resulting in underestimates of true distribution volumes.

Although the percentage of circulating drug which is bound to proteins is influenced to some extent by drug concentration, the degree of binding by most drugs is constant over the normal therapeutic range.

The binding of individual drugs to plasma proteins is difficult to determine accurately, and reported values often vary from different laboratories. It is convenient therefore to differentiate compounds into those which are highly bound (80–100%), moderately bound (50–80%), and weakly bound (<50%). Some parenteral antimicrobial agents which fall into these categories are listed in Table III (5).

TABLE III. Plasma Protein Binding of Some Antimicrobial Agents (5)

1. *Highly bound* (80–100%)	
Oxacillin	Erythromycin
Nafcillin	Lincomycin
Cefazolin	Clindamycin
Doxycycline	Chlortetracycline
2. *Moderately bound* (50–80%)	
Penicillin G	Cefoxitin
Carbenicillin	Cephalothin
Ticarcillin	Minocycline
Cefamandole	Chloramphenicol
3. *Weakly bound* (<50%)	
Methicillin	Gentamicin
Cefuroxime	Amikacin
Cephaloridine	Tetracycline
Cefotaxime	Streptomycin

As drug which is bound to plasma proteins is essentially restricted to the plasma volume, the degree of binding may influence drug availability to extravascular sites. For example, drug which is protein bound cannot cross the blood-brain barrier. However, the once popular notion that highly bound drugs cannot reach extravascular sites, has been shown to be incorrect for many compounds. For example, the cephalosporins cefazolin and cephalothin are 75–85% bound to plasma proteins, and yet have larger apparent distribution volumes than cephalexin and cephaloridine, which are only 20% bound to plasma proteins. This relationship is shown in Figure 2. Clearly, the binding of compounds to tissue proteins and other extravascular macromolecules also plays an important role in drug distribution.

Two other compounds which are highly

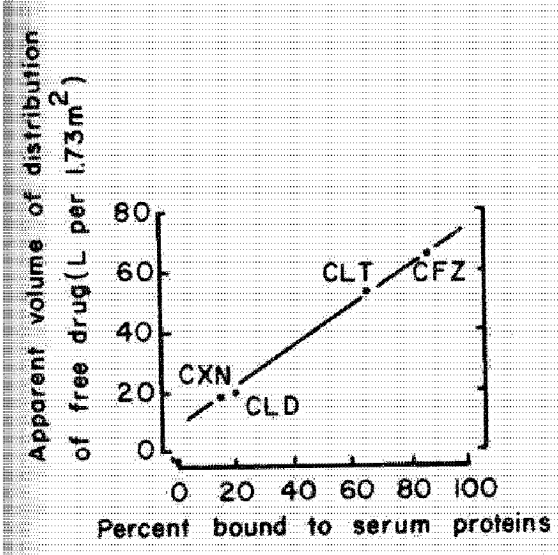

Figure 2—The relationship between serum protein binding and the distribution volume of free drug for four different cephalosporins. CFZ = cephazolin, CLT = cephalothin, CLD = cephaloridine, and CXN = cephalexin. Correlation coefficient = +0.998. Reproduced, by permission, from Clin. Pharmacokinet., **2**, 252–268 (1977).

bound to plasma proteins, and yet distribute extensively into extravascular tissues and fluids, are erythromycin and trimethoprim. While erythromycin is 90% bound, and trimethoprim 60% bound to plasma proteins, more than 95% of the total body load of both of these compounds is distributed in extravascular tissues and fluids. Changes in drug binding, due to drug–drug interactions or disease conditions, may cause drug redistribution in the body. These types of changes, however, are of clinical significance only for drugs which are normally highly bound to plasma proteins.

Drug Elimination

Drugs are eliminated from the body primarily by hepatic metabolism and/or renal excretion. Other mechanisms, usually less important, include excretion via the bile, lungs, sweat, saliva, and breast milk. The elimination characteristics of each drug depend largely on its physico-chemical properties. In general, water-soluble drugs are readily cleared by the kidneys, while lipid-soluble compounds are primarily metabolized in the liver.

The rate at which drug elimination occurs is a function not only of the intrinsic ability of the eliminating organ to handle a particular drug but also of the drug distribution volume and binding characteristics.

For drugs that are eliminated by glomerular filtration, plasma protein binding delays their excretion, since only unbound drug is filtered. Similarly, hepatic metabolism is retarded because bound drugs generally do not have access to metabolic sites. On the other hand, plasma protein binding has no direct effect on kidney tubular secretion, because of the rapid dissociation of drug–protein complex during the drug secretion process.

Within the usual range of therapeutic levels for many drugs, elimination is a first-order process, the rate being proportional to the concentration of drug in plasma, and governed by the elimination rate constant k_{el}. For drugs which are cleared wholly or partially by hepatic metabolism however, saturation of drug metabolizing enzymes may occur at high drug concentrations. Under such circumstances, metabolism is governed by Michaelis-Menten kinetics as:

$$\text{Rate of metabolism} = \frac{V_{max} \cdot C}{K_m + C} \quad \text{(Eq. 5)}$$

where C is the concentration of drug at the metabolic site, V_{max} is the maximum velocity at which a particular metabolic step can occur, and K_m is the Michaelis-Menten constant. From this equation it is clear that, at low drug concentrations the rate of metabolism is approximated by $V_{max} \cdot C/K_m$ or $k_{el} \cdot C$, where $k_{el} = V_{max}/K_m$, i.e., a pseudo first-order rate. At high drug concentrations however, the rate of metabolism is approximated by $V_{max}C/C = V_{max}$. This is the maximum velocity with which the metabolic step can occur, and the process becomes zero-order in nature. Two compounds that undergo this type of saturable elimination in the therapeutic concentration range are phenytoin and salicylate.

Effect of Pharmacokinetic Behavior on Drug Bioavailability

The plasma profile of an administered drug

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