PARENTERAL FUNDAMENTALS

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

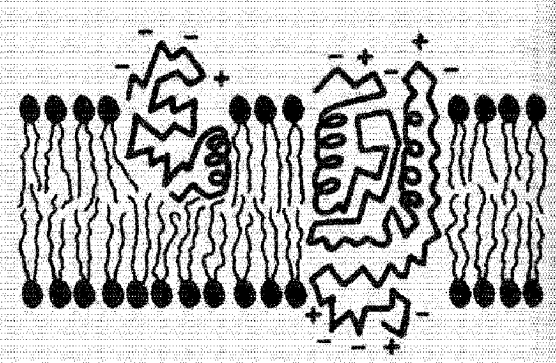


Figure 1—The lipid-globular protein mosaic model of membrane structure: schematic cross-sectional view. The phospholipids are depicted as a discontinuous bilayer with their polar heads oriented outward. The integral proteins are shown as globular molecules partially embedded in and protruding from the 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

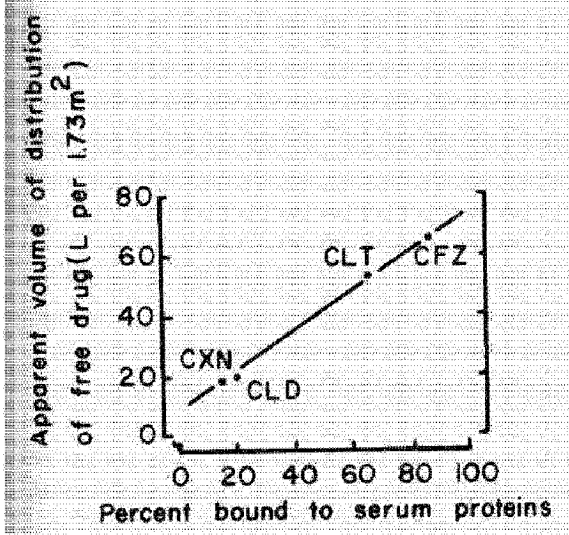


Figure 2—The relationship between serum protein binding and the distribution volume of free drug for four different cephalosporins. CFZ = cephazolin, CLT = cephalothin, CLD = cephaloridine, and CXN = cephalexin. Correlation coefficient = +0.998. Reproduced, by permission, from Clin. Pharmacokinet., **2**,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

is affected by the rate and extent of absorption, the rate of elimination and also the drug distribution volume. The types of effects that may occur are summarized in Figure 3. Decreasing the absorption rate will result in lower and more prolonged drug levels, with no change in the overall area under the drug-level curve. Similar variations in drug profiles may be obtained with variable absorption rates when drug appearance is zero-order in nature. As in the first-order case, slower zero-order, or constant rate, release of drug over a prolonged period will result in lower but more prolonged circulating drug levels. Decreasing the fraction F of drug which is available to the circulation however, results in lower drug levels and a reduced area under the drug-level curve, the reduction being directly proportional to the fraction of bioavailable drug. A reduction in the elimination rate constant k_{el} will result in increased and more prolonged drug levels, and the degree by which levels are increased also becomes greater with repeated doses. A change in drug distribution may affect circulating drug levels, the concentration of drug in plasma being inversely related to distribution volume. However, the clinical implications of this type of change depend on whether the site of drug action is within the vascular compartment and those body fluids in equilibrium with the vascular compartment, or in other tissues. The apparent distribution volume of digoxin in man is approximately 500 liters, due to extensive tissue binding. In severe uremia however, the distribution volume decreases to 200 liters. However, the action of digoxin on the myocardium appears to be associated with tissue drug levels, so that a similar plasma digoxin level in a uremic individual to that in a person with normal renal function may be associated with a reduced relative therapeutic effect.

Of the four parameters considered in Figure 3, the two values commonly affected by drug bioavailability characteristics are the efficiency of absorption, F, and the rate constant for appearance of drug into the circulation k_a, or k_0 when appearance is zero-order in nature.

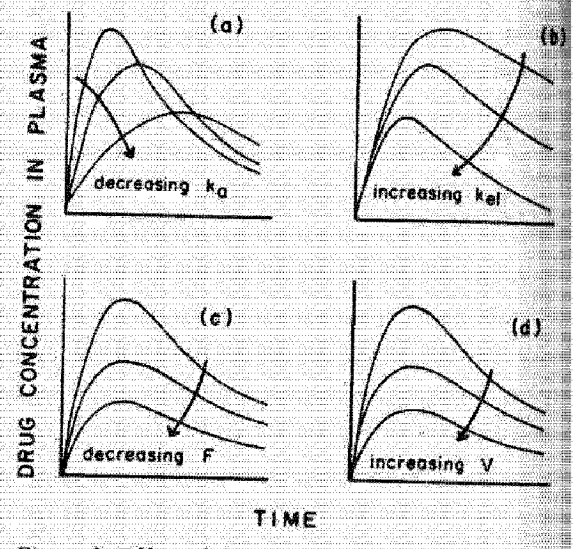


Figure 3—Effect of changes in (a); the absorption rate constant k_a, (b); the elimination rate constant k_{el} (c); the fraction of dose absorbed F, and (d); the drug distribution volume V on circulating drug profiles.

Intravenous Administration

Introducing the drug directly into the venous circulation results in complete drug bioavailability, but the shape of the plasma drug profile is determined by the rate of injection. A bolus injection (Fig. 4) gives an almost instantaneous peak plasma level, and this dosage route is useful when a prompt response is de-

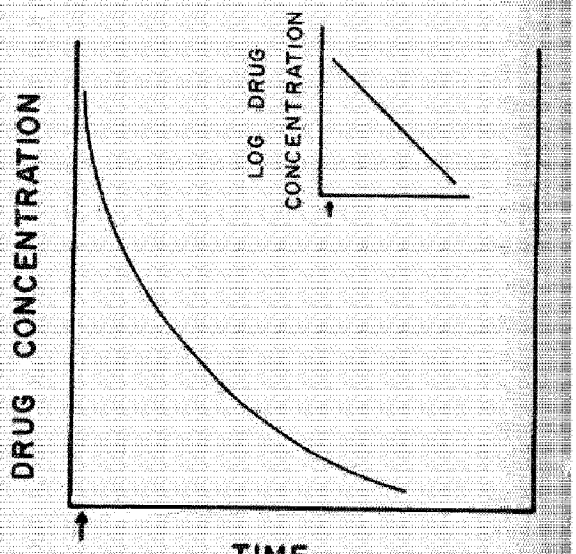


Figure 4—The plasma concentration vs. time curve for a drug which is administered by bolus intravenous injection, and is eliminated in first-order manner. The insert shows the same curve plotted on a semilogarithmic scale.

sired. A good example of this method of administration is the use of intravenous lidocaine in the emergency treatment of ventricular arrhythmias, encountered during cardiac surgery or resulting from myocardial infarction.

The duration of action of a drug in the body is affected by its half-life. The anesthetic effect of a single intravenous dose of thiopental [$t_{1/2}$ = 49 min (6)] disappears within minutes. The anti-cancer agent 5-fluorouracil is another drug with an extremely short half-life [$t_{1/2}$ = 10 min (7)]. On the other hand, drugs with long half-lives such as digoxin [$t_{1/2}$ = 42 hr (8)] have a prolonged duration of action.

While the duration of a drug in the body is not necessarily related to its bioavailability, the drug half-life does affect the area under the plasma concentration vs. time curve, *AUC*, which is a parameter commonly used as an index of drug bioavailability. The relationship between the *AUC* value and other pharmacokinetic parameters is shown in Eq. 6:

$$AUC = (1.44)F \cdot D \cdot t_{1/2}/V \quad \text{(Eq. 6)}$$

where $t_{1/2}$ is the drug biological half-life and V its distribution volume in the body. It is clear that, besides its dependence on F, D, and V, the *AUC* is also directly proportional to $t_{1/2}$, so that any variations in this value must be taken into consideration when the *AUC* is used in bioavailability assessment.

The intravenous route should not be used to deliver drugs with low aqueous solubility, which may precipitate in blood and cause embolism. Another major disadvantage of the intravenous route is that once injected, the dose cannot be withdrawn. It is therefore injected slowly, over a period of 1 to 2 min, or longer, to avoid excessively high transient concentrations of drug in plasma, which may produce undesirable cardiovascular and central effects.

Precise and continuous drug therapy is provided by intravenous infusion at a constant rate, which can be controlled by using an intravenous drip or an infusion pump. Generally, flow rates of 2 to 3 ml per minute are employed. This method is particularly useful for drugs with a narrow therapeutic index, and when the effective blood levels are well defined, as in the case of aminophylline in treating asthma. Adequate bronchodilation with minimum adverse effects is usually achieved within an aminophylline plasma concentration range of 8 to 20 μg/ml (9).

The circulating steady-state drug level C_{ss} which is achieved during intravenous infusion is related to the infusion rate k_0, the drug distribution volume V, and its biological half-life, as in Eq. 7:

$$C_{ss} = (1.44)\, k_0 \cdot t_{1/2}/V \quad \text{(Eq. 7)}$$

The value of C_{ss} increases in direct proportion to both the drug infusion rate and the drug half-life, but is inversely proportional to the distribution volume. Clearly, if the infusion rate or the drug biological half-life is doubled, the latter being due perhaps to saturable metabolism or competition by some other drug for elimination mechanisms, then C_{ss} will also be increased to twice the original value.

While the steady-state drug level achieved by an intravenous infusion is thus influenced by several factors, the time taken to reach the steady-state is controlled by only one factor, the drug half-life in the body. Regardless of the rate at which a drug is infused, it will take approximately 4.5 drug half-lives to approach steady-state levels. This may be particularly important for drugs with long biological half-lives. For example, comparing the drugs already mentioned in the intravenous injection case, steady-state levels of 5-fluorouracil will be achieved within one hour of the start of infusion, while it will take up to 8 days to achieve steady-state circulating levels of digoxin.

The above concepts apply also to drugs which are given intermittently, for example by repeated intravenous or intramuscular injection. Regardless of the way in which a drug is administered, it will take four to five drug biological half-lives to reach steady-state levels in the bloodstream.

For many drugs which have long biological half-lives, loading doses have to be administered at the start of therapy in order to avoid

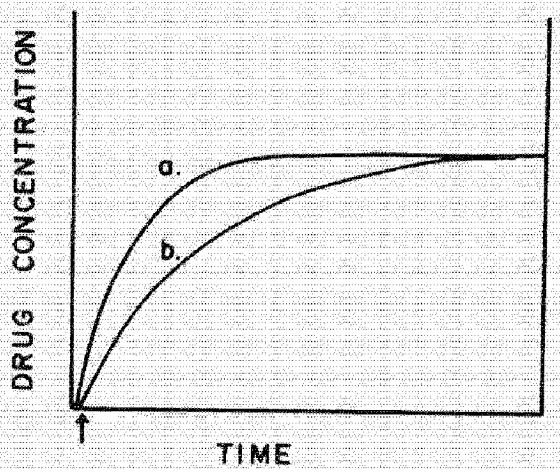


Figure 5—Plasma concentration vs. time curves for drugs with (a) a short biological half-life, and (b) a long biological half-life during continuous intravenous infusion. The infusion rates are adjusted according to Eq. 7 to obtain the same C_{ss} values.

the delay in achieving the desired drug levels in the body. Typical plasma profiles during intravenous infusion of drugs which have short and long biological half-lives are shown in Figure 5.

Intramuscular Administration

Intramuscular injection usually, but not always, provides quantitative drug delivery to the body with less hazard than the intravenous route. Drug effects are less rapid, but generally of longer duration. The intramuscular route

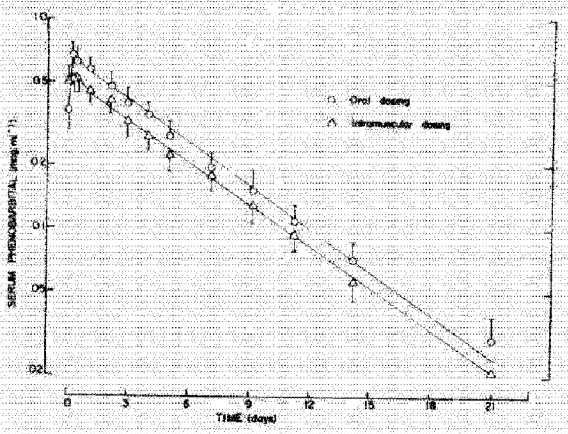


Figure 6—Mean serum levels of phenobarbital during 21 days following single oral doses of phenobarbital (30 mg) and single intramuscular injections of sodium phenobarbital (equivalent to 27.4 mg phenobarbital). Bars indicate one standard error (n = 5). Reproduced, by permission, from J. Clin. Pharmacol., ***18***, *100–105 (1978).*

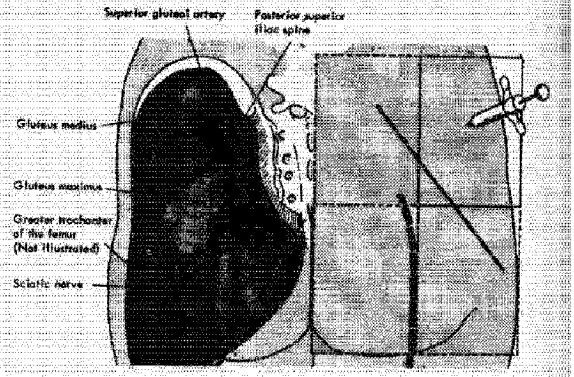
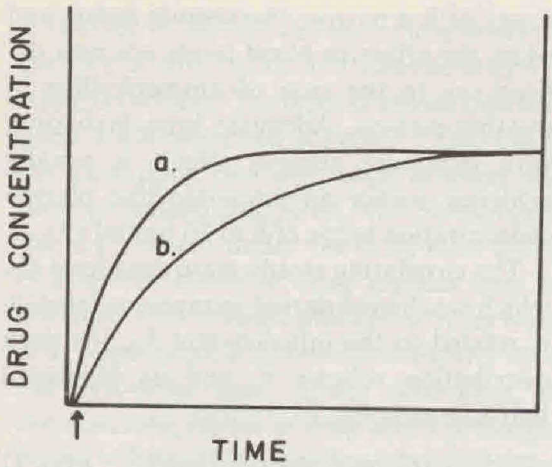


Figure 7—Injection site in gluteus muscle. This figure, and also Figures 8, 9, and 10, are reproduced by permission from R. D. Musser and J. J. O'Neill, Pharmacology and Therapeutics, *4th ed., Macmillan, New York, NY, 1971.*

is often used to administer drugs that are poorly absorbed from the gastrointestinal tract. For example, piperacillin, a new semisynthetic aminobenzyl penicillin derivative which is poorly absorbed orally, is rapidly and reliably absorbed after intramuscular administration (10).

However, drugs are not always completely available following intramuscular injection. Slow or incomplete absorption from intramuscular sites has been reported for chlordiazepoxide, diazepam, digoxin, phenytoin, and phenobarbital, and the extent of absorption may also be influenced by the patient's age. Although phenobarbital appears to be completely bioavailable following intramuscular injection to children, it is only 80% available compared to oral doses in adults (11). Serum levels of phenobarbital obtained during 21 days following oral and intramuscular doses are shown in Figure 6. Note the very long duration of this drug in serum from both dosage routes. The biological half-life of phenobarbital from these data was approximately 90 hours.

Intramuscular injections are made deep into the skeletal muscles, preferably far away from major nerves and blood vessels. In adults, the upper portion of the gluteus maximus is a frequently used site for this purpose. In infants and young children, the deltoid muscles of the upper arm or the midlateral muscles of the thigh are usually preferred. The usual sites for



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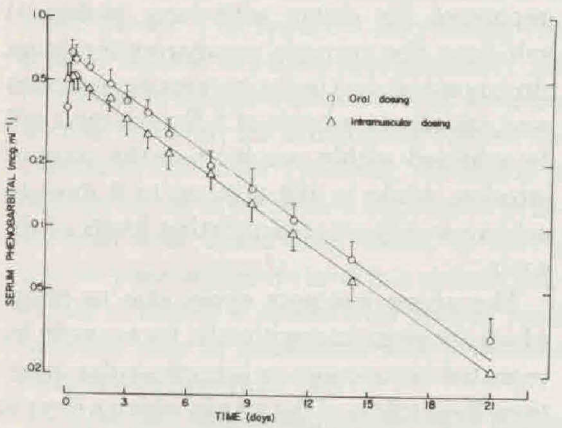

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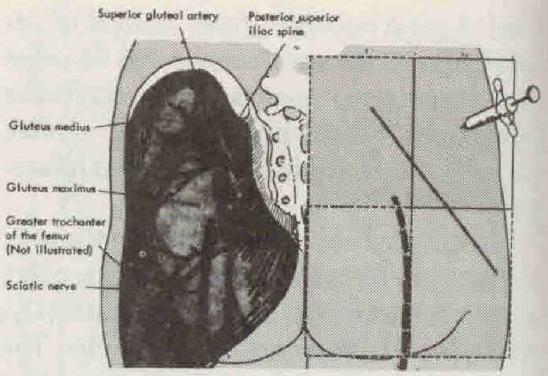

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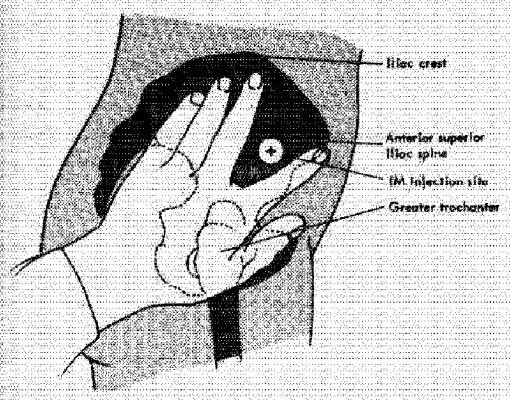


Figure 8—Anterior gluteal injection. The injection site is located by placing one finger on the iliac spine and the thumb or another finger just below the iliac crest with the palm of the hand on the hip. There is considerable muscle mass, and no large blood vessels or nerves, in this area.

intramuscular injection are shown diagramatically in Figures 7–10.

Aqueous or oleaginous solutions or suspensions of drugs may be administered intramuscularly. The absorption rates vary widely depending on the type of preparation used, as well as on other biopharmaceutical factors. These have been discussed in some detail in a review article by Ballard (12).

Some compounds, i.e., penicillins and cephalosporins, may cause considerable pain when injected intramuscularly and are often given intravenously whenever possible. Cephalothin is particularly painful when given intramuscularly and this drug is routinely given by the intravenous route.

The primary factors which influence the

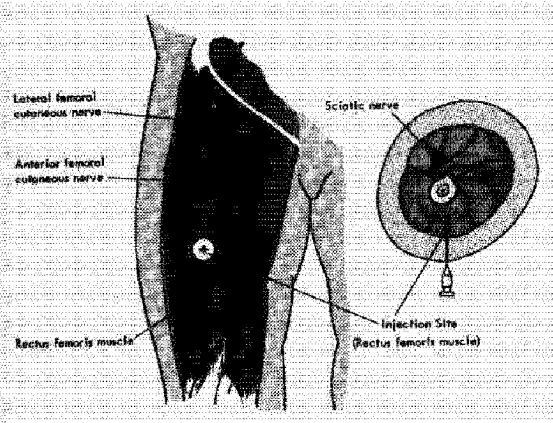


Figure 9—Injection site in midanterior region of the thigh.

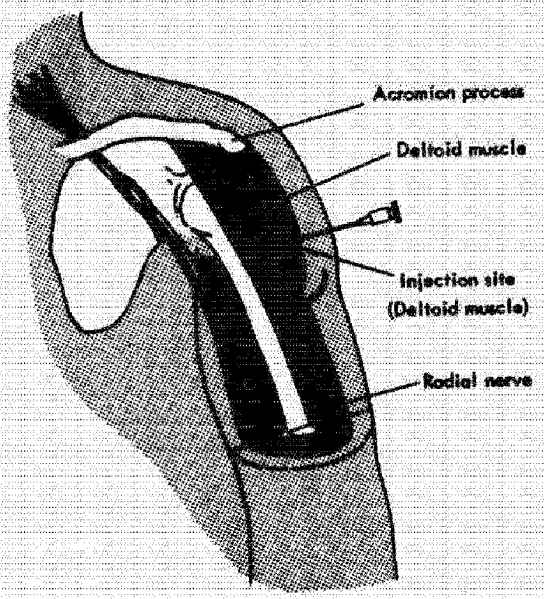


Figure 10—Injection site in the deltoid muscle below the acromion process.

rate and extent of intramuscular drug absorption are summarized in the following sections.

Solubility of Drug

When solutions of sparingly soluble acids and bases are injected into the muscle, they are gradually buffered to physiological pH. This pH shift may cause the drug to precipitate at the injection site, often resulting in prolonged absorption as the precipitated drug slowly redissolves in the tissue fluids. An example is the precipitation of quinidine base after an intramuscular injection of quinidine hydrochloride solution. Precipitation of drug at the injection site, and slow resolubilization to yield low and possibly undetectable drug levels in the bloodstream, may also explain the apparently incomplete bioavailability of intramuscular phenobarbital and other compounds discussed earlier. Clearly, the injection of larger aqueous fluid volumes will minimize drug precipitation at the injection site but there are practical limits to the actual volume injected, particularly in children.

Solvent Effect

Drugs which are poorly water-soluble, e.g., diazepam, can be dissolved in non-aqueous

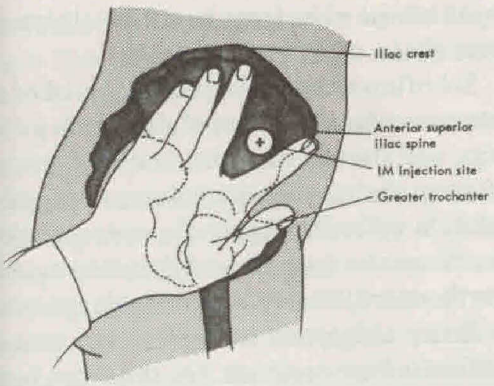


Figure 8—Anterior gluteal injection. The injection site is located by placing one finger on the iliac spine and the thumb or another finger just below the iliac crest with the palm of the hand on the hip. There is considerable muscle mass, and no large blood vessels or nerves, in this area.

intramuscular injection are shown diagramatically in Figures 7–10.

Aqueous or oleaginous solutions or suspensions of drugs may be administered intramuscularly. The absorption rates vary widely depending on the type of preparation used, as well as on other biopharmaceutical factors. These have been discussed in some detail in a review article by Ballard (12).

Some compounds, i.e., penicillins and cephalosporins, may cause considerable pain when injected intramuscularly and are often given intravenously whenever possible. Cephalothin is particularly painful when given intramuscularly and this drug is routinely given by the intravenous route.

The primary factors which influence the

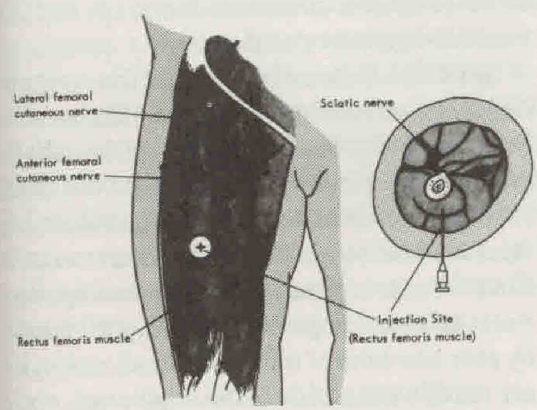
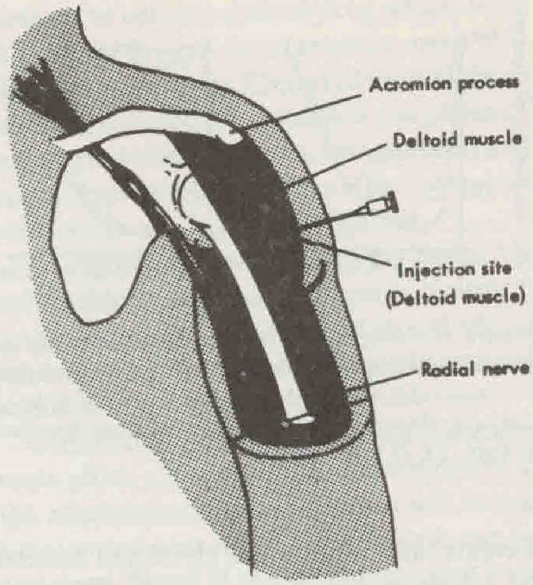


Figure 9—Injection site in midanterior region of the thigh.



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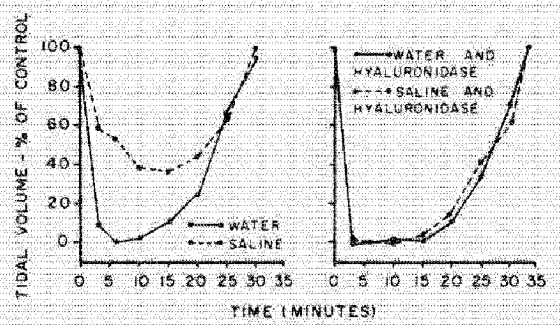

Figure 11—Respiratory tidal volumes following intramuscular administration of 4 mg/kg succinylcholine in various solvents. Each curve is the mean of 10 to 12 subjects. Reproduced, by permission, from Anesthesiology, ***23,*** *213–218 (1962).*

solvents such as propylene glycol and mineral oil, which may or may not be miscible with water. The water-miscible solvents are removed from the intramuscular site more quickly and the drug may precipitate, again resulting in low and prolonged blood levels.

The solution of a drug in saline is more hypertonic than a solution in water and the saline vehicle may cause a greater flow of water toward the injection site, resulting in slower absorption. The greater effect of succinylcholine on respiratory tidal volume when injected intramuscularly in a water solution, compared to a saline solution, is shown in Figure 11 (13). The figure shows also that the solvent effect is obliterated by addition of hyaluronidase. This had the effect of increasing the absorption of succinylcholine from the saline solution, due to improved fluid absorption and diffusion, while having little influence on drug absorption from the water solution.

Volume and Concentration of Injection Solution

More rapid absorption is generally obtained when drugs are administered in a smaller injection volume. This phenomenon may be explained in terms of mechanical compression of adjacent capillary beds by large injection volumes, a disproportionate ratio between increase in surface area and increased volume, and the relatively long diffusion path to be travelled by molecules from the center of the injection site when large injection volumes are used (14).

Schriftman and Kondritzer (15) studied the intramuscular absorption of atropine in guinea pigs, and showed that for a constant amount of drug, the smaller the volume of injection solution (thus the higher the concentration) the faster the drug cleared from the muscle. Furthermore, smaller injection volumes result in faster absorption even when the concentration is kept constant. On the other hand, varying concentrations of drug in the same intramuscular injection volume had little effect on absorption rate. Similar observations in rats have been reported for the neutral, pharmacologically inert sugars mannitol and sucrose (16).

The volume of medication which can be administered by the intramuscular route in humans is, of course, limited and varies from a maximum of 5 ml in the gluteal region to 2 ml in the deltoid of the arm.

Molecular Size

The blood capillary wall behaves as a lipoid-pore layer, allowing lipid-soluble substances to penetrate readily through the entire surface. In contrast, water-soluble compounds appear to pass through water-filled pores (although these have never been positively identified) whose total area is far less than the capillary surface.

Consistent with these theories, lipid-soluble molecules are rapidly absorbed from intramuscular injection sites, while the absorption of water-soluble molecules is erratic, and dependent on molecular size.

Sund and Schou (16) studied the systemic absorption of mannitol (mol. wt. 182), sucrose (mol. wt. 342), inulin (mol. wt. 3000–4000), and dextran (mol. wt. 60,000–90,000) from rat thigh muscle and found that the absorption rates are inversely related to molecular weight. These results lend support to the concept that water-soluble compounds cross capillary walls by pore size-limited diffusion. Small molecules are readily absorbed via the capillaries, while larger molecules must enter the circulatory system indirectly via the lymphatics. They are

thus limited in their absorption by the slow lymph flow which is only 0.1% of plasma flow.

Vascular Perfusion

A major rate-limiting factor in intramuscular drug absorption is often the flow of blood through and around the injection site. Blood flow rates range from 0.02 to 0.07 ml/min per gram of muscular tissue. The higher the blood flow rate, the higher the clearance rate of the drug from the injection site, and the greater the rate of drug absorption. For example, absorption of lidocaine is rapid after injection into the arm muscle but slow from the gluteus maximus, largely because of differences in blood flow. Differences in blood flow may also be responsible for the more rapid intramuscular absorption of cefuroxime (17), cephradine (18), and some other compounds in men than in women, due to the greater fraction of adipose tissue in females (19). In a study in children with diabetes mellitus, Nora and associates (20) showed that the mean absorption half-life for ^{131}I-labelled lente insulin was 224 min and 314 min after arm and thigh injections respectively.

Rubbing the skin around the injection site increases local blood flow and therefore the absorption rate. Furthermore, rubbing favors the spread of the medication throughout a wider area of tissue, thus increasing the area for absorption to take place. Exercise also increases blood flow to skeletal muscles, by as much as 15- to 20-fold. During rest, only about 10% of the muscle capillaries are open. During strenuous exercise, however, a greater proportion of the capillaries open, allowing increased blood flow (21). Muscular movement is also known to increase the flow of lymph fluid through the lymph vessels. On the other hand, drug absorption rate tends to decrease in disease states such as shock, hypotension, and congestive heart failure, which may reduce the blood flow around the site of injection.

Sustained Release Intramuscular Formulations

Various aspects of the use of physical methods to obtain sustained drug release from implanted devices have recently been discussed in a review by Chien (22) to which the reader is referred for a detailed discussion of polymeric delivery systems, encapsulated and matrix-type vehicles, and the effect of system parameters on drug release profiles.

An ideal implanted drug delivery device has to be stable in, and compatible with, biological tissues. It must be nontoxic, and should release the drug at a constant rate for a predetermined period.

Compared to oral dosing, the intramuscular route offers a more controlled environment at the administration site, with a much longer time period over which drug release can be sustained. Some of the approaches that have been used for this purpose are summarized below.

Aqueous Suspensions

At the intramuscular injection site of an aqueous suspension, drug is continuously dissolving to replenish that which is being carried away (absorbed). Benzathine penicillin, procaine penicillin, and also insulin–zinc suspension, are examples of drugs injected as water-soluble suspensions for the purpose of providing gradual and controlled release over a prolonged time period. Controlled release can be achieved by varying the particle size of the drug, which has a direct effect on mean dissolution rate, according to the Noyes-Whitney equation. Sedimentation of suspensions is avoided by adjusting the viscosity of the vehicle. Due to practical constraints imposed by syringeability and pain upon injection, the solid contents of intramuscular suspensions should not exceed 5% of the total volume and the particle size should be below 10 μm.

In addition to adjusting the particle size (dissolution), prolonged release also may be achieved by altering the solubility of a drug, often with salt, derivative, or complex formation. For example, the decanoate ester of fluphenazine shows prolonged release from an intramuscular depot injection when administered in sesame oil to dogs (23).

Oily Vehicles

The release of drug from an intramuscular oily solution is controlled by the partitioning of drug from the oil into the surrounding aqueous medium. Absorption is therefore dependent largely on the drug oil/water partition coefficient.

Based on similar principles, oily suspensions and oil-in-water or water-in-oil emulsions have been investigated as alternative means of providing controlled drug release. The number of oils that can be used for intramuscular dosage is limited, and includes almond oil, arachis oil, castor oil, cottonseed oil, and olive oil (24). Oily injection vehicles have been used primarily to achieve sustained release of some oil-soluble vitamins and hormones. For example, intramuscular vasopressin tannate as an oily suspension has a prolonged duration of action between 48 and 96 hrs.

The main disadvantage of oily injection vehicles is that they tend to remain in tissue as oily cysts long after the absorption of active drug. Of the vehicles which have been used, olive oil is absorbed most rapidly, while castor oil appears to remain in tissue almost indefinitely. The various oils also differ somewhat in their inflammatory response.

Complex Formation

A drug may be reversibly bound as a dissociable complex with macromolecules such as methylcellulose or polyvinylpyrrolidone. Assuming that only free (unbound) drug is absorbed, release of the drug can be controlled by using an appropriate concentration of the macromolecule. Drug will be released as absorption continues, according to the characteristic dissociation constant of the complex. Compounds administered in these types of vehicles include dexamethasone acetate, hydrocortisone acetate, and prednisolone acetate.

Another type of complex used to promote sustained drug release acts by decreasing the solubility of drug at the injection site. Complexes such as protamine zinc insulin, ACTH zinc tannate, and cyanocobalamin zinc tannate provide slow release of macromolecules due to this type of interaction, with a relatively small complexing agent.

Polymer Matrix Suspensions

These are relatively new, and to a large degree experimental, methods intended for sustained drug release (24). Typically, drug is suspended in a biodegradable polymer such as poly(lactic acid) and injected in an aqueous solution of carboxymethylcellulose. Investigations with narcotic antagonists and antineoplastic agents have shown that drug release from these systems is limited by dissolution of the drug–polymer matrix, and drug release rate is inversely related to particle size. The rate of drug release from this type of system can thus be controlled, in theory at least, by appropriate modification of polymer particle size.

Microencapsulation and Liposomes

The use of microencapsulation, the coating of drug particles with a degradable polymer, has recently been shown to have potential to achieve prolonged release after parenteral dosage (24). Intramuscular injection of microencapsulated forms of fluphenazine embonate, and also of gold sodium thiosulfate, have resulted in 2-fold increases in their duration of activity (25, 26).

The use of liposomes, which consist of drug entrapped within concentric aqueous and nonaqueous bilayers, is being examined as a means of providing controlled drug delivery to particular body organs, particularly the liver and spleen where most liposome degradation occurs. Although to the writers' knowledge liposomal preparations have not yet been used in intramuscular dosage form, the potential of this method of drug administration may be realized when the use of liposomes as a general controlled-release dosage form becomes more clearly established.

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