# Bioavailability of Parenteral Drugs II. Parenteral Doses Other Than Intravenous and Intramuscular Routes

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## *Introduction*

In the previous article of this series basic pharmacokinetic principles governing drug levels in blood were reviewed, and the bioavailability of parenteral drug products was described with particular reference to intravenous and intramuscular dosage forms (1). In this article attention is focused on the bioavailability of dosage forms which are administered by other parenteral routes.

The major drugs and drug groups which may be administered by parenteral routes other than intravenous and intramuscular are shown in Table I. In many instances, e.g., subcutaneous insulin and intraarterial or intrathecal administration of anticancer compounds and antibiotics, the parenteral dosage route is well established and clinically useful. In other instances, such as intradermal vaccines and vaginal administration of estrogens for systemic activity, the dosage route is less well established but has considerable clinical potential for some compounds.

## *Subcutaneous Administration*

Many compounds are routinely given by subcutaneous injection, in particular insulin, local anesthetics, and vaccines.

Small volumes (0.5 to 2 ml) of medications in solution form may be administered by subcutaneous (hypodermic) injection, usually into the outer surface of the upper arm, although the anterior surface of the thigh, abdomen, or buttock may also be used. The needle is usually inserted at a 45-degree angle to the skin, as shown in Fig. 1.

The same factors affecting intramuscular drug absorption also govern drug bioavailability following subcutaneous doses (2). The rate of absorption, $R_t$, of a subcutaneous dose of drug from the injection site into the blood is proportional to the amount of drug at the site, $A_s$, as described by Eq. 1:

$$R_t = p(A_s) \qquad \text{(Eq. 1)}$$

The penetration coefficient, $p$, depends upon the diffusion coefficient of the drug in the particular environment, the area of membrane exposed to the solution, the distance of diffusion, and the concentration gradient of drug across the absorption membrane. The primary absorption membrane in subcutaneous connective tissue is the capillary wall (3).

As with intramuscular doses, drug solutions injected subcutaneously are influenced by the buffer capacity of the subcutaneous tissues

TABLE I. Compounds Which May be Administered by Parenteral Routes Other Than Intravenous and Intramuscular

| Route | Compounds |
|---|---|
| Subcutaneous | Bethanechol, epinephrine, fat-soluble vitamins, heparin, insulin, local anesthetics, vaccines |
| Intradermal | Antigens, vaccines |
| Percutaneous | Nitroglycerin ointment, safflower oil |
| Intraarterial | Anticancer agents, vasopressin |
| Intrathecal | Antibiotics, anticancer agents, local anesthetics |
| Intraperitoneal | Antibiotics, anticancer agents, insulin |
| Inhalation | Anesthetic gases, antibiotics, atropine, corticosteroids, cromolyn sodium, epinephrine, ergotamine, isoproterenol, lidocaine, metaproterenol, terbutaline |
| Vaginal | Estrogens, progesterone, prostaglandins |

and fluids (4). The rate of absorption of subcutaneous lidocaine hydrochloride, for example, is affected by pH changes at the injection site (5). At a pH of 7.4, the lidocaine hydrochloride concentration must be lower than 0.097% to avoid precipitation.

Absorption of drugs which are given subcutaneously is generally slower than after intramuscular administration because of less efficient regional circulation. Prolonged absorption of metallic mercury from subcutaneous injections was demonstrated in a recent case of metallic mercury poisoning (6).

Molecules or ions with low molecular weights are absorbed primarily via the capillaries, while molecules having high molecular weights appear to be absorbed primarily via lymph vessels (7). Hyaluronidase, an enzyme

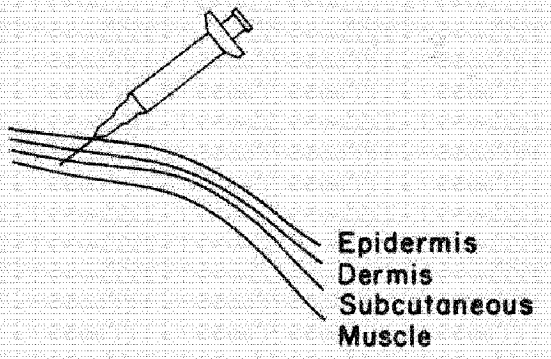


*Figure 1—Subcutaneous injection.*

which breaks down mucopolysaccharides of the connective tissue matrix, has been used to promote spreading of solutions and to increase drug absorption rates (8).

Drug absorption is increased by rubbing the skin around the injection site, and also by exercise. Berger and associates (9) reported a substantial increase in the absorption rate of $^3$H-insulin due to leg exercise following subcutaneous injection leading to markedly elevated plasma levels of exogenous insulin. The effect of exercise on circulating $^3$H-insulin levels in one patient is shown in Fig. 2. The effect is more pronounced when insulin is injected into an exercised limb than when it is injected at another site (10). This is illustrated in Fig. 3 which shows a far greater increase in hypoglycemic effect due to leg exercise when

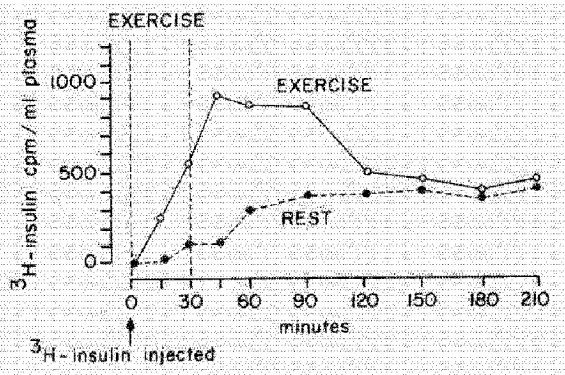


*Figure 2—Effect of mild bicycle exercise on plasma levels of intact $^3$H-insulin following subcutaneous injection of 4 × $10^5$ cpm $^3$H-insulin/kg body weight into the leg of a juvenile patient. Reproduced by permission from Diabetes (Suppl. 1),* **28,** 53–57 (1979).

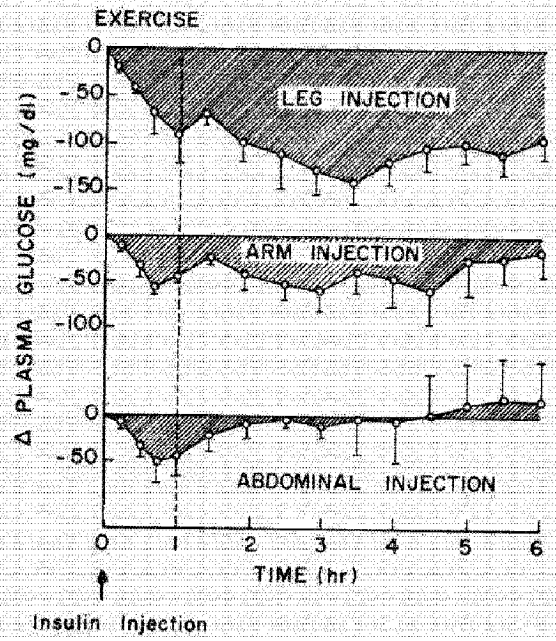


*Figure 3—Influence of injection site on plasma glucose response to insulin during leg exercise. Shaded areas represent changes in plasma glucose levels (mean ± SE) following insulin injection during leg exercise compared to that obtained with no exercise. The area above the curve for leg injection is significantly greater than those for both arm ($p < 0.02$) and abdominal ($p < 0.005$) injections. Reproduced by permission from N. Engl. J. Med.*, **298**, 79–83 (1978).

insulin is injected subcutaneously into the leg compared to the arm, while the effect was negligible after abdominal injection. Stimulation of absorption could be due to changes in the interstitial fluid pressure of subcutaneous tissue owing to contractions of underlying musculature or movements of the injected limb.

Drug action may be prolonged if injection is made deep into the subcutaneous tissue, e.g., aqueous solutions of heparin and long-acting insulins. Coadministration of epinephrine with local anesthetics extends their duration of local action by producing vasoconstriction in the zone of absorption (11). Cooling also causes local vasoconstriction and results in prolonged drug absorption.

### *Sustained-Release Subcutaneous Products*

Prolonged release of drug may be obtained by implanting pellets under the skin. An ideal pellet does not disintegrate but slowly dissolves in the subcutaneous fluid environment during the implantation period. The absorption rate of drug can be determined by weighing the pellet upon removal (12). For a spherical pellet,

$$W = \frac{\pi\rho}{6}(D^0 - kt)^3 \qquad \text{(Eq. 2)}$$

and for a flat disc,

$$W = \frac{\pi\rho}{4}(D^0 - kt)^2(h^0 - kt) \qquad \text{(Eq. 3)}$$

where $W$ is the weight of pellet at any time $t$ after implantation, $\rho$ is the apparent density of solid, $D^0$ is the initial diameter of the sphere or disc, $h^0$ is the initial height of the disc, and $k$ is the mean absorption rate constant.

Subcutaneous implants have been used in commercial products for the continuous delivery of certain steroid hormones, e.g., testosterone (Oreton), and the delivery of a variety of drugs, including benzyl penicillin, gold salt, progesterone, and sulfadiazine, from subcutaneous implants has been tested in man or experimental animals (12, 13). Silastic rubber implants have been examined for re-

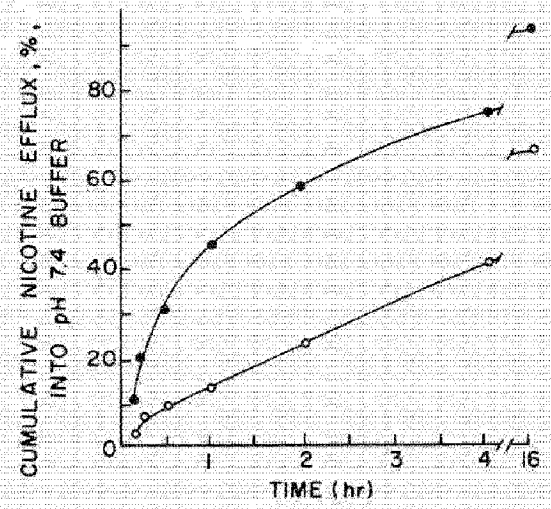


*Figure 4—Cumulative percentage of nicotine base released from dimethylpolsiloxane (-●-) and dimethylpolysiloxane + fluorosilicone-laminated polysiloxane (-O-) tubings into pH 7.4 buffer at 37°. Reproduced by permission from J. Pharm. Sci.*, **63**, 1849–1853 (1974).

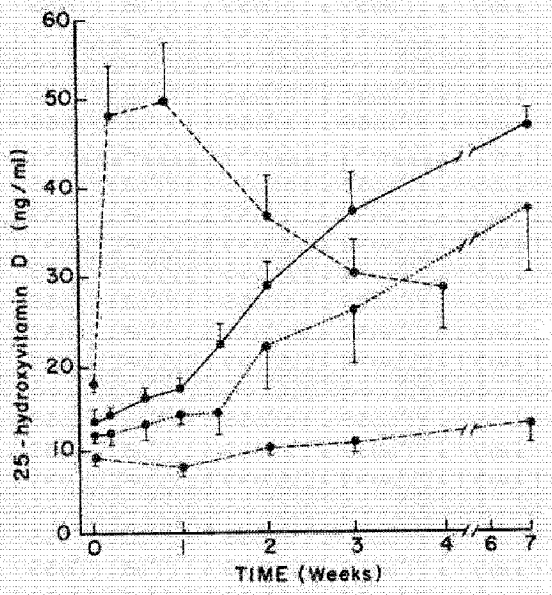


*Figure 5—Serum 25-hydroxyvitamin D levels (± SEM) in volunteers who received a 100-μg/kg oral dose (●--●), a 200-μg/kg intramuscular dose (●—●), or a 200-μg/kg subcutaneous dose (● . . . ●) of vitamin D, and in control subjects who received no vitamin D (●-·-●). Reproduced by permission from J. Clin. Endocrinol. Metab.*, **48**, 906–911 (1979).

lease of progestogens (14), and Gaginella and associates have demonstrated marked variation in the rate of drug release from different silicone polymers (15). This is illustrated in Fig. 4, in which the in vitro release of nicotine base into pH 7.4 buffer from a dimethylpolysiloxane polymer reaches 75% in 4 hr and 95% in 16 hr, but the release from a fluorosilicone-laminated polymer is reduced to 40% in 4 hr and 65% in 16 hr. The use of polymer materials with different release characteristics is of considerable potential in the design of sustained-release drug implants. Alginate implants have been shown to provide slow and continuous release of fluoride in rats (16), while oily depot subcutaneous injections resulted in prolonged release of vitamin D (17). Comparative serum levels of the metabolite 25-hydroxyvitamin D during a 7-week period following oral, depot intramuscular, and depot subcutaneous doses of vitamin D, and also in control animals who received no vitamin D, are show in Fig. 5.

Marked differences in the in vitro release of

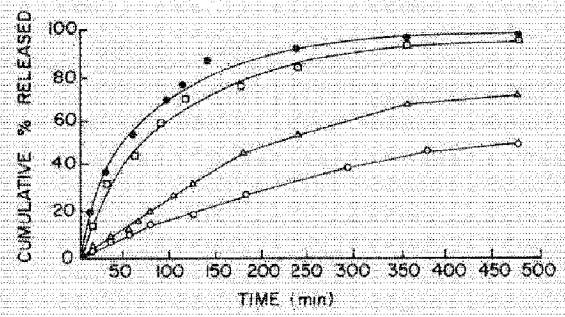


*Figure 6—In vitro release of pentagastrin from two liquid formulations, I (-●-) and II (-□-), and from two crystalline suspensions, III (-△-) and IV (-○-) into pH 7.3 isotonic phosphate buffer at 37°. Reproduced by permission from J. Pharm. Pharmacol.*, **22**, 923–929 (1970).

pentagastrin from two solutions (Formulations I and II) and two crystalline suspensions (Formulations III and IV) designed for subcutaneous injection are demonstrated in Fig. 6 (2). Prolonged release of pentagastrin from the subcutaneously injected crystalline formulations is suggested in Fig. 7, in which biliary excretion of drug was lower but more prolonged from Formulations III and IV than from Formulations I and II.

Although still in the early stages of devel-

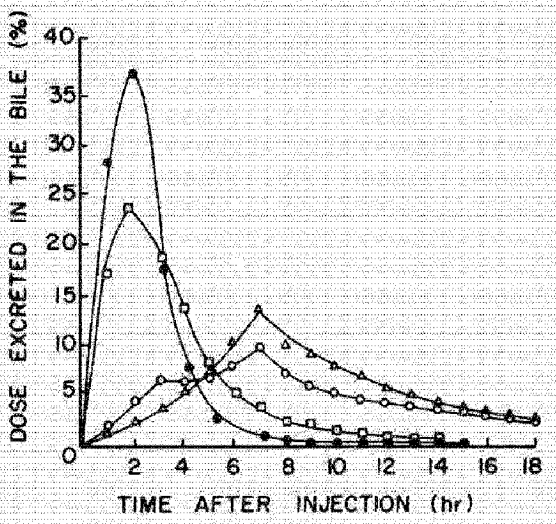


*Figure 7—Biliary excretion of radioactivity labelled pentagastrin after subcutaneous administration of liquid formulations, I (-●-) and II (-□-), and crystalline suspensions, III (-△-) and IV (-○-) to rats. Reproduced by permission from J. Pharm. Pharmacol.*, **22**, 923–929 (1970).

opment, liposomes appear promising as potential vehicles for delivering drugs from the site of subcutaneous injection to specific targets within the body. Liposomes are hydrated liquid crystals formed when phospholipids are allowed to swell in aqueous media. In a recent study (18) unilamellar vesicles consisting of distearoyl phosphatidylcholine, cholesterol, and some sugar and amino-sugar derivatives of cholesterol were shown to be potentially useful in developing liposome systems capable of providing controlled release of therapeutic agents.

*Intradermal Administration*

Intradermal injections are used predominantly for local effects, but the potential of this route for systemic activity, particularly for vaccines, has been illustrated in several studies.

Intradermal injection is made into the upper layers of skin, just beneath the epidermis. A usual site for intradermal injection is the anterior surface of the forearm. The volume of solution that may be administered in this manner is only about 0.1 ml.

Intradermal injection is frequently used for administering antigens in tests for allergic reactions (19). Alcohol is given by intradermal injection for the treatment of pruritus vulvae (20). While systemic absorption from an intradermal injection site is usually slow, this route is useful in delivering agents for immunization (21). An intradermal injection of 0.1 ml of an Asian influenza vaccine produces a rise in antibody titer comparable to that achieved with a subcutaneous injection of 1 ml of the same vaccine (22, 23). A recent study by Halperin *et. al.* (24) confirmed the superiority of the immunogenicity of the intradermal route for A/Victoria/75 vaccine, but failed to show any difference in intradermal and subcutaneous routes for A/New Jersey/76 (Swine Flu) vaccination. The authors concluded that in times of vaccine shortage the intradermal route, which involves smaller doses, may be important. In addition, less local irritation may be associated with intradermal than with subcutaneous injections (25).

*Percutaneous Administration*

The outermost layers of human skin consist of the epidermis and the dermis (see Fig. 1). Drugs penetrate the epidermis at rates determined largely by their oil/water partition coefficients, water-soluble molecules being virtually excluded. The underlying dermis consists of loosely arranged connective tissue and is more freely permeable. Various pharmacokinetic models have been examined to describe the percutaneous absorption of a drug from topically applied vehicles (26, 27). The percutaneous route is used primarily in situations where drug action is to be upon an open wound or upon the superficial layers of the stratum corneum. If the pathologic condition is in the deeper layers of the epidermis or in the dermis, topical drug therapy may be ineffective. For example, antibacterial and antifungal agents are often more effective in skin infectious when given orally or by injection than when applied to the skin.

Two examples of the use of percutaneous absorption for systemic effects are the topical application of safflower oil in some patients with essential fatty acid deficiency who cannot be dosed parenterally, and topical nitroglycerin ointment for the prevention or treatment of angina. Accurate titration of the dose of nitroglycerin is achieved by adjusting the amount of ointment to the patient's needs. The usual dose is 1–2 in., as squeezed from the tube, every 3 to 4 hr (28).

*Inhalation*

The respiratory tract has been used as a route of drug administration for centuries and the large number of compounds which may be administered by this route is indicated in Table I. This pathway consists of the mouth or nose, pharynx, trachea, bronchi, bronchioles, alveolar ducts, alveolar sacs, and the alveoli. Together, they provide an extremely large surface area for rapid absorption, most of which occurs in the alveolar ducts and alveolar sacs. For a more complete description of the anatomy and physiology of the respiratory system, the reader is referred to a review by Gorman and Hall (29).

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