Physiological Pharmaceutics

Barriers to drug absorption

Second Edition

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however a number of indications for smaller doses, such as myocardial oxygenation during coronary angioplasty, show some promise. The field has been recently reviewed by Krafft and coworkers (1998)[14].

ii) Haemoglobin-based products. Free haemoglobin resulting frim lysis of erythrocytes is cleared rapidly from the circulation; large amounts of haemoglobin will cause kidney damage. Two approaches are being studied to prevent renal excretion; modification and encapsulation. The modified route uses polymerized or cross-linked haemoglobin, usually treated with glutaraldehyde or coated with polyethylene chains[15]. Rabinovici and coworkers[16] and others have studied the possibility of encapsulating haemoglobin in liposomes to make an artificial red cell.

INTRAMUSCULAR DELIVERY

Physiology

Intramuscular delivery involves the injection of the dose form into a muscle, from where it is absorbed due to the perfusion of the muscle by blood. The formulation forms a local depot which is partly mixed with interstitial fluid, and partly forms a bolus within the muscle, particularly if the injected volume is large. As a result it is important to realize that the injection is made into abnormal tissue; this may be particularly important if the formulation is intended to reside in the body for a significant length of time.

The structure of a typical muscle is shown in Figure 2.3. The muscle is wrapped in a connective sheath called the epimysium, within which are bundles of individual fibres, each surrounded by a connective membrane termed the perimysium. A finer matrix of connective fibrous tissue, the endomysium (omitted from Figure 2.3 for clarity), surrounds the muscle fibres, and the blood capillaries run within the endomysium, largely in a longitudinal manner, with numerous cross-connections. As a result the whole muscle is extremely well perfused. There are also numerous lymphatic vessels, but these lie in the epimysium and perimysium.

The preferred sites for injection are the gluteal, deltoid, triceps, pectoral and vastus lateralis. The deltoid muscle is preferred due to its greater perfusion rate compared to the other muscles, although the vastus lateralis has the advantage of having fewer major blood vessels into which the injection might accidentally be placed. When an intramuscular injection is administered, it is normal practice to withdraw the syringe plunger briefly to see if blood can be withdrawn. Blood indicates that the needle may be in a vessel, and the injection should be repositioned. There is also a minor danger of damaging a nerve fibre during the injection.

Pharmacokinetics

The most significant advantage of intramuscular delivery is the ease with which a wide range of drugs can be administered in a variety of dosage forms, which not only provide rapid absorption, but can also be used for sustained therapy. Intramuscular delivery involves a number of steps (Figure 2.4); i) release of the drug from the dose form into the intercellular fluid (ICF), ii) absorption from the ICF into the blood and lymphatics, iii) transport from the local blood volume into the general circulation, and iv) metabolism. The concentration of drug and kinetic profile are determined by the relative rates of these processes, and we should note that the capillary membrane is highly permeable and in general will not be rate-limiting, but perfusion of the muscle by the blood may be significantly slower. We can distinguish two particular limiting cases of interest:

i). Injection of a bolus of soluble drug. In this case the drug is immediately available in the ICF and is rapidly absorbed into the capillaries. In this case the rate-limiting absorption step is the perfusion of the muscle by the blood. Any factor which influences muscle perfusion (such as movement or exercise) will change the rate of absorption. In particular,

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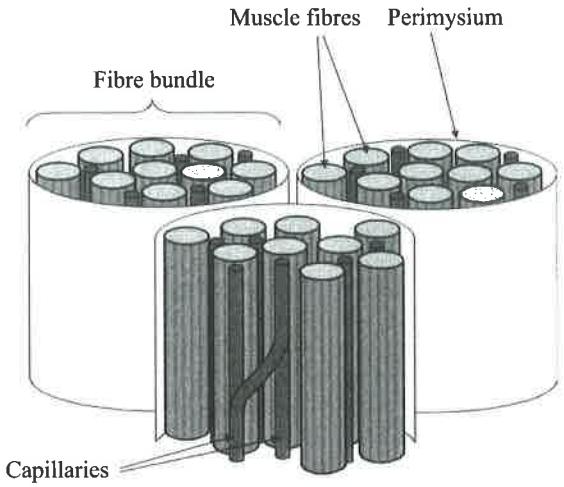

Figure 2.3 Schematic structure of muscle

if cardiac failure has occurred, absorption will be extremely low since the muscle perfusion rate will be small. For this reason intramuscular delivery is contra-indicated if cardiac function is poor.

ii) Injection of the drug in sustained-release form (e.g a solid depot or crystal suspension). In this case release from the formulation is slower than absorption or perfusion, and so the behaviour of the device becomes the rate-limiting step, and the effects of muscle perfusion are not evident. Under these conditions the concentration of drug in the plasma remains approximately constant until the delivery device is exhausted, a period which can be designed to last from several hours to several months.

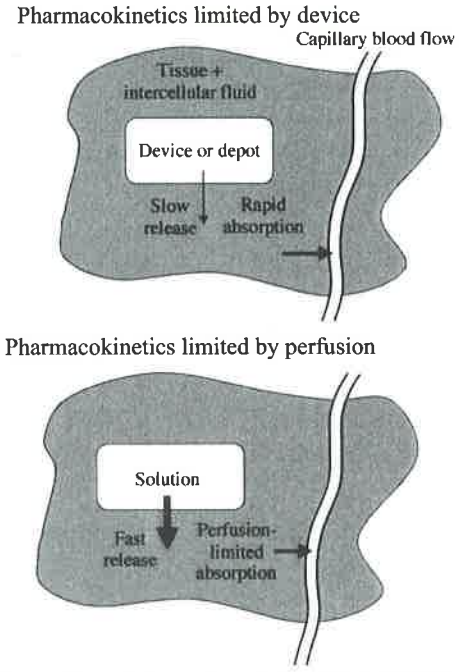

Figure 2.4 Absorption of drugs from intramuscular injections

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Formulation considerations

Since the formulation does not have to be miscible with water, it is possible to inject a much wider range of materials than those which can be administered intravenously. The possible formulations include aqueous solutions, aqueous suspensions, oily solutions, oil in water emulsions, water in oil emulsions, oily suspensions, and dispersions in polymer or solid implants. These are listed approximately in order of release rate, as aqueous solutions can be absorbed in minutes, while implants can deliver drugs for several months.

In addition a range of other factors can influence the absorption rate. If the drug is extremely hydrophobic it will not dissolve in the ICF, while if it is strongly ionized or extremely water soluble it will not be able to cross the capillary membrane. Drugs which are strongly protein-bound will also be slowly absorbed since their activity in solution will be reduced. A number of drugs administered in solutions may be absorbed anomalously slowly if the composition of the formulation changes after injection. For example, phenytoin is formulated as an injection at pH 12 due to its low solubility. On injection the ICF quickly reduces the pH to normal levels, and the drug precipitates. As a result it may then take several days for the dose to be fully absorbed.

SUBCUTANEOUS DELIVERY

Physiology

A subcutaneous injection (SC) is made into the connective tissue beneath the dermis, and should be contrasted with an intradermal injection which is made into the dermal layer, often between the dermis and the epidermis (Figure 2.5). This is a critical distinction because the subcutaneous tissues have a significant volume of interstitial fluid into which the drug can diffuse, while the epidermal tissue has relatively little available fluid, nor is it well perfused by blood. As a result an intradermal injection persists at the site for a long period and the available volume for injection is small; it is normally used for antigens (e.g. tuberculin) and vaccines (smallpox).

Drugs injected subcutaneously dissolve in the interstitial fluid and gain entry to the bloodstream by two routes. They may be absorbed directly into blood vessels, but the subcutaneous tissues are often adipose and poorly perfused. Alternatively the interstitial

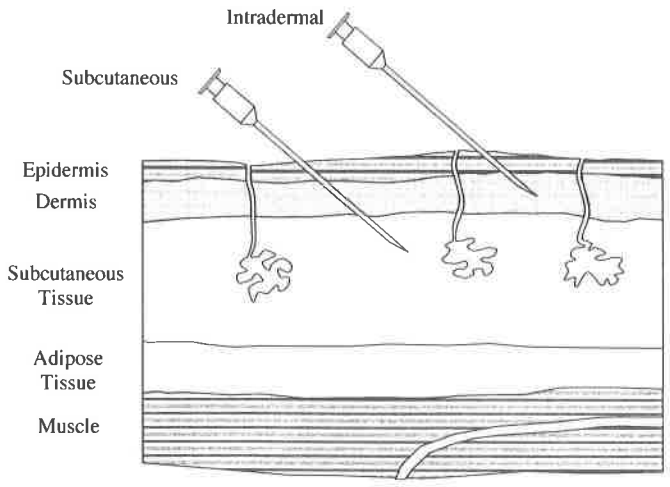

Figure 2.5. Physiology of parenteral administration routes

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