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Invited Review

Release and absorption rates of intramuscularly and subcutaneously injected pharmaceuticals (II)

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Abstract

The rate and extent of intramuscular (i.m.) and subcutaneous (s.c.) drug absorption are very erratic and variable. The lipophilicity of the compound plays an important role. Aqueous drug solutions and suspensions of the more lipophilic compounds are often absorbed incompletely within the therapeutically relevant time. More hydrophilic compounds are absorbed completely. Injection depth, drug concentration and vehicle volume, pH-pK_a relation, vehicle, cosolvents and surfactants have strong influences on the absorption profile of lipophilic drugs. Aqueous solutions of hydrophilic drugs are less sensitive to these factors. Drug solutions in oil and even suspensions in oil are often thought to be sustained release preparations. In fact, rapid absorption has often been observed. Slow release is not a property of the oily vehicle but is achieved by a high lipophilicity of the dissolved or suspended compound. Liposomal preparations are currently under investigation as i.m. and s.c. injectable sustained release preparations. Factors that induce drug release at the injection sites are the proteins and especially lipoproteins in the interstitial fluids, originating from serum filtrate and from turnover of inflammatory cells. Phagocytosis by macrophages and fat cells may play an important role in the local clearance of liposomal material from the injection site. Sustained release of some pharmaceuticals with normal or long half-lives appeared in specific cases preferable to rapid release. In addition, high arterial drug concentrations during the absorption phase may result in undesired effects even when venous drug concentrations are within the safe range.

Key words: Drug absorption; Intramuscular administration; Subcutaneous administration; Absorption rate

1. Introduction

The intramuscular and subcutaneous routes of drug injection are often used when drugs cannot be injected intravenously because of their low aqueous solubility and/or when high peak concentrations, resulting in local or systemic side effects, occur with intravenous injection. Moreover, additional advantages of these routes include greater convenience, less problems with compatibility of the injection components with full blood in the ciculation and often less frequent administration when compared to intravenous administration.

Many variables are known to affect drug release after intramuscular or subcutaneous injection. Factors such as molecular size, pK_a, drug

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solubility, initial drug concentration, injection depth, body movement, blood supply at the injection site, injection technique and properties of the vehicle in which the drug is formulated have been discussed extensively in a previous review (Zuidema et al., 1988). This article is an update with emphasis on factors related to drug transport through the tissue, the role of drug lipophilicity, recent technology to modulate drug absorption from intramuscular and subcutaneous injection sites by carrier systems such as liposomes, absorption by the lymphatic system and clinical implications.

Drugs such as antibiotics, anti-asthmatics, anticonvulsics, anxiolytics and analgesics are often administered intramuscularly in severe disease states. A generally held viewpoint is that the drug is rapidly and completely absorbed from the injection site. Previously published data have already demonstrated that complete absorption during a time relevant for therapy is not true in every case (Ballard, 1968; Dundee et al., 1974; Kostenbauder et al., 1975; Tse and Welling, 1980), however, recognition of their significance is lacking. Such findings may have important clinical implications.

Consequently, this article is aimed at reviewing the relevant literature, in order to provide and to discuss material for the rational design of intramuscular and subcutaneous drug formulations and to examine the clinical aspects of these types of injections. In contrast to the former review which was organised in order of the types of injection, this article is mainly ordered with respect to elements of the mechanism and further subdivided in types of injection.

2. Drugs in conventional systems

Conventional systems are solutions, emulsions and suspensions in aqueous or in oily vehicles.

2.1. Drugs in rapidly releasing systems

2.1.1. Aqueous injections; variability in absorption rate

It has frequently been reported that absorption after intramuscular and subcutaneous injection is very variable (Gibaldi, 1977). This is first illustrated with some aqueous solutions.

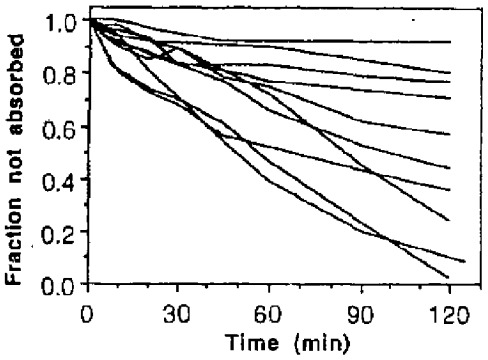

Fig. 1. Fraction remaining to be absorbed after intramuscular injection of 20 mg/kg sodium artelinate aqueous solution in rabbits ($n = 10$).

Artelinic acid is a water-soluble derivative of artemisinin, an antimalarial drug, of the fast-acting schizontocidal type. Artemisinin and its derivatives are important new drugs, especially for the treatment of life-threatening states of the disease. Artelinic acid is even more active than artemisinin itself, but is very rapidly eliminated after intravenous injection. Rapid and complete absorption is therefore essential. After intramuscular injection in rabbits the absorption rate appears to be very variable (Titulaer et al., 1993). This is depicted in Fig. 1 where the fractions not absorbed are plotted vs time.

The curves representing the fraction remaining to be absorbed suggest an apparent zero-order absorption. This is a rather unexpected phenomenon, since diffusion is characterised by a first-order mechanism. A possible explanation is a solvent flow dependent paracellular transport of this highly hydrophilic solute. This transport capacity is very variable, at least between subjects, and it appears that it is influenced by several factors including muscle activity, inflammation and flow of the tissue fluid (Zuidema et al., 1988a). This explanation is supported by the next example.

Relevant information on kinetic behaviour of i.m. and s.c. injections has often originated from

veterinary studies. The risk of residual drug at injection sites is a considerable problem in meat consumption. Fig. 2 shows as a second example the large variation in absorption parameters after intramuscular and subcutaneous injection, in a fat-rich region, also referred to as intra-adipose injection (Kadir et al., 1990a). Carazolol is a β-blocking agent which is used in veterinary practice as a tranquillising agent in cattle and pigs. The fraction of carazolol absorbed during the first 24 h from an aqueous solution varied from 24 to 59% after intramuscular and from 25 to 66% after intra-adipose injection.

Many factors which influence the variability in the rate and extent of absorption can be postulated. Firstly, a difference between intra- and intermuscular injection is postulated and defined as injections within and between the muscle fibrils, respectively (Groothuis et al., 1980). Such a supposition must be supported by a bimodal statistical distribution in absorption rate. In the literature, however, experimental evidence for this contention is lacking. Secondly, differences in drainage and blood flow are possible explanations. The cause of these differences, however, remains unclear. Thirdly, differences in absorption rate might also be result from differences in osmolality and other formulation factors, however, such factors cannot explain variability with the same preparation and batch. Physiological circumstances that vary randomly and physiological reactions to the injection trauma might influence absorption.

A more likely explanation than those mentioned above is a variation in the shape of the depot. The shape may vary from merely spherical to almost needle-shaped in different subjects. These differences depend on the local cohesion between the muscle components and the tendency to be torn open by the injection procedure. Differences in shape are accompanied by differences in the depot surface (and therefore in the effective permeation area), the interface between depot and tissue and the absorption rate.

2.1.2. Drug lipophilicity in aqueous systems; extent of absorption and absorption rate

Lipophilic compounds are slowly absorbed from intramuscular and subcutaneous injection sites (Zuidema et al., 1988). Recent findings show that absorption under such conditions often seems to be incomplete as well. It appeared that the apparent half-lives of midazolam in patients after intramuscular injection are much longer than after intravenous injection, due to rate-limiting sustained release from the intramuscular injection site (Raeder and Nilsen, 1988). In a former study by the same group, a reduced apparent bioavail-

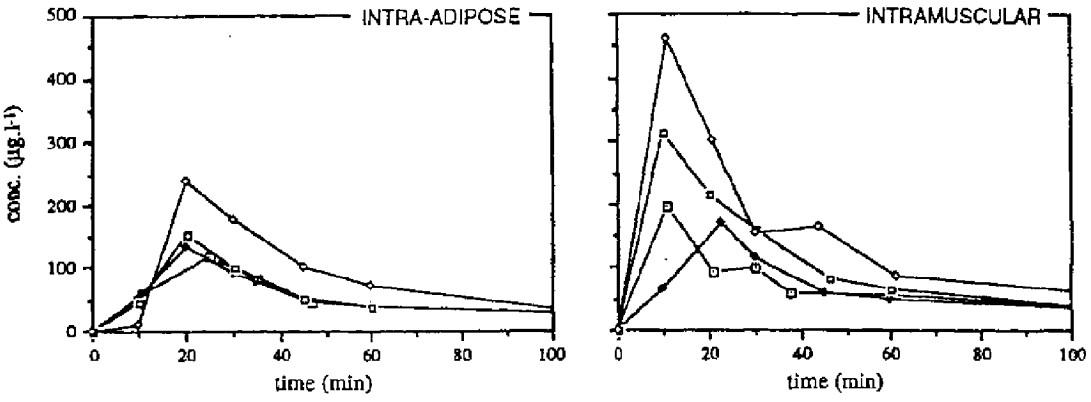

Fig. 2. Individual concentration-time curves of carazolol in the serum of four pigs following intramuscular and subcutaneous administration of 0.025 mg/kg in a fat layer (intra-adipose injection).

ability of midazolam under these conditions was also observed (Raeder and Breivik, 1987).

Phenobarbital appeared to be completely absorbed after intramuscular injection in deltoid muscle in children, however, the bioavailability was only 80% relative to oral administration in adults (Viswanathan et al., 1978). Nevertheless, the number of investigated subjects was too small to permit definite and statistically warranted conclusions. A lack of stability of phenobarbital (the amide bonds might be hydrolysed at the injection site) might be proposed as an explanation for the incomplete bioavailability. This possibility cannot excluded, however, it does not explain the difference between children and adults nor the findings in the midazolam study. Further information is needed for a better understanding of the factors which determine bioavailability in these specific cases.

The β-blocking agents are an ideal group for studying drug lipophilicity and release from intramuscular and subcutaneous injection sites, since they have similar molecular weights and pK_a values but differ markedly in lipophilicity. Studies in pigs using crossover experiments with propranolol, atenolol, carazolol, metoprolol and alprenolol have recently been published (Kadir et al., 1990a,b).

The curves representing the fraction remaining to be absorbed of the β-blocking agents, constructed from intramuscular and subcutaneous (intra-adipose) plots and using intravenous data as references, demonstrate biphasic declines; a rapid first phase followed by a very slow second phase (Fig. 3). Initial release rates appeared to be negatively correlated with drug lipophilicity expressed as fat-buffer partition coefficients, especially after injection in the subcutaneous fat layers, also called intra-adipose layers. Propranolol showed greater and faster absorption than expected from its lipophilicity only after intramuscular, but not after intra-adipose, injection. Propranolol is known to possess irritating properties which may improve blood perfusion in the muscles and account for the deviation in behaviour after intramuscular injection. The subcutaneous fat layer or adipose layer is less sensitive to such irritating properties and is less perfused.

The extent of drug release within the mentioned 24 h also transpired to be dependent on the lipophilicity of the compound: the more lipophilic the compound, the lower the bioavailability at 24 h after injection (the observation period) (Fig. 4). The most hydrophilic compound, atenolol, was the only one which was completely absorbed or bioavailable within 8 h after intramuscular injection and within 24 h after subcutaneous injection (Fig. 3).

Injected drugs are probably rapidly absorbed, provided sufficient vehicle is present to maintain the drug in solution or to drive the absorption process. After the vehicle has been absorbed the

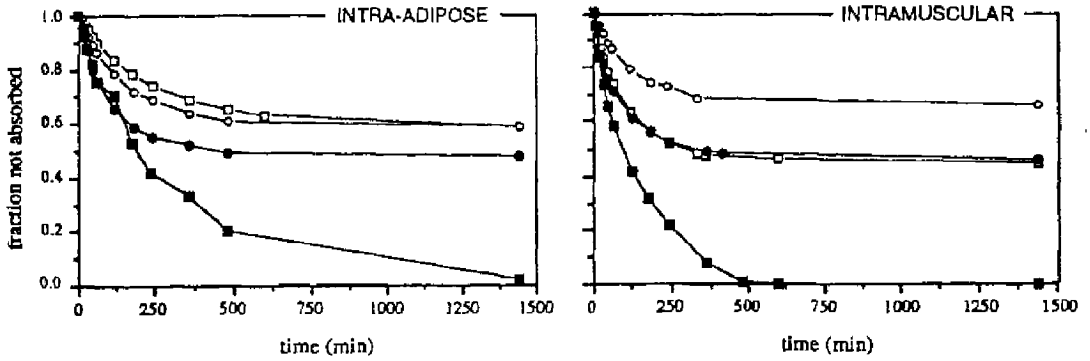

Fig. 3. Fraction remaining to be absorbed curves (drug vs time) after intramuscular and intra-adipose administration of a series of β-blocking agents. (□) Propranolol, (○) alprenolol, (●) metoprolol, (■) atenolol.

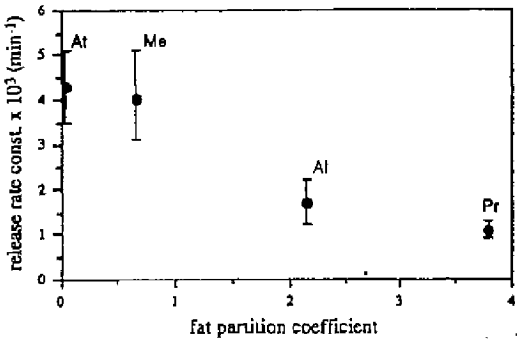

Fig. 4. Correlation between the fat-buffer distribution constants and release rates on intra-adipose administration of atenolol (At), metopropol (Me), alprenolol (Al) and propranolol (Pr).

absorption rate of the drug decreases rapidly. This theory explains the midazolam studies but is also relevant in the case of the rapid absorption of artemisinin from an intramuscularly injected suspension in oil and the low and erratic absorption of artemisinin from a suspension in water as shown in the following (Fig. 5).

2.1.3. Oily injections; influence of the lipophilicity of the vehicle on the absorption rate

The next example is an oily injection. Artemisinin is rather lipophilic and not soluble in water, however, it is also sufficiently insoluble in oil to allow its preparation as a dissolved injection as of a conventional oil system with a sufficiently high dose.

Oil systems and suspensions for injection are generally considered to be sustained release formulations. Therefore, the rapid onset of absorption shown in Fig. 5a with the artemisinin suspension in oil is striking (Titulaer et al., 1990b). The oily vehicle is absorbed only very slowly and remains present at the injection site for several months. Apparently, artemisinin dissolves rather rapidly in the oil phase and the dissolved fraction is then depleted by further absorption. In the case of artemisinin, this depletion is apparently a rapid transit process over the oil to the water interface to the tissue fluids. This is less favoured in the case of highly lipophilic substances.

In contrast to the oily system, the rate of dissolution of artemisinin in the aqueous injection is slow and the process appears to cease almost completely within the first few hours, the time during which the aqueous vehicle has been absorbed.

In the preceding section, studies have been discussed in which the lipophilicity of a drug or model compound was the variable in a given aqueous medium. Interestingly, a study has appeared in which the drug was chosen as the constant and the lipophilicity of the oily vehicle was the variable (Table 1) (Al-Hindawi et al., 1986). The in vivo release of testosterone propionate in a number of oily vehicles was investi-

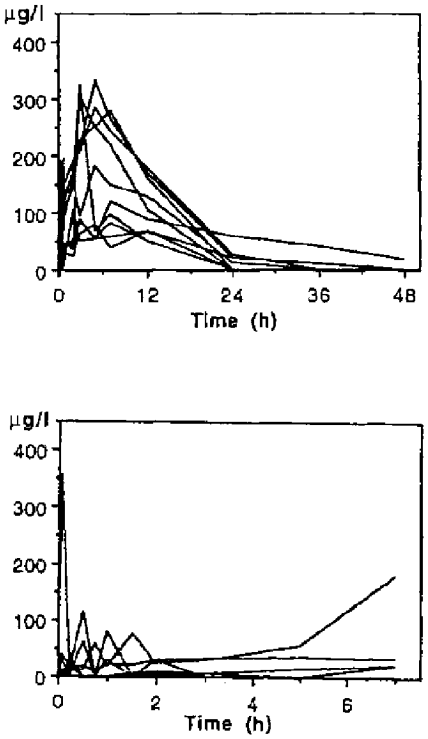

Fig. 5. Plots of artemisinin concentrations in serum vs time ($n = 10$) after a dose of 400 mg artemisinin to human volunteers: (a) suspension in oil intramuscularly; (b) suspension in an aqueous vehicle intramuscularly.

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