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**Review Article**

# Release and absorption rate aspects of intramuscularly injected pharmaceuticals

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## Summary

Injection depth is an important parameter influencing absorption rate after intramuscular injection. A too shallow injection will, especially in the gluteal region, only reach the subcutaneous fat layer. This fat layer appears to exert a retarding effect on lipophilic drugs, which is moreover dependent on formulation factors. A cohesive mechanistic description of the variables and their interrelationships does not exist. From a review study on the relevant information it appears that the mean absorption times of drugs in aqueous or oily suspension i.m. injected is longer (weeks to months) than of drugs in solution (minutes to hours, incidentally weeks, dependent on the lipophilicity of the drug). The injection depth is an important variable since the mean absorption times are considerably longer when the drug is shallowly injected in the adipose layer. In intramuscular injection kinetics the following steps are considered to be important (in hierarchical sequence): dissolution rate, solvent supply (vascularisation or perfusion), phase transfer and diffusion to the vascular system, all of them more or less susceptible to formulation, physiological variables and injection depth (in fat or muscular tissue). Dissolution and solvent supply are associated with zero order-, phase transfer and diffusion processes with first order release and absorption kinetics. In general a "mixed" order appearance in the circulation will result from a more complicated situation. After application to mucosal membranes such as buccal and vaginal walls many lipophilic drugs appear to show a depot effect resulting in larger mean absorption times (the order of magnitude is hours) than hydrophilic drugs. A similar phenomenon is seen in the intramuscular absorption. The differences can be explained by the nature of the retaining bonds and differences in histological structure. It can be concluded that the subcutaneous adipose layer has important retarding effects on the absorption of drugs which are intentionally or otherwise injected in the adipose layer.

## Introduction

The i.m. route of drug injection is important especially for drugs, which can not be injected i.v., e.g. because of their low aqueous solubility.

With drugs in suspension and advanced technical methods or with the use of colloidal drug carriers it is possible to prepare controlled release systems for i.m. use. I.m. controlled-release injections are often given to avoid high peak levels and related toxicity of drugs with a small therapeutic index, or they are given to reduce the dose frequency in order to improve patient compliance. As important examples of controlled release injections the neuroleptics, contraceptive steroids, depot antibiotics, depot chemotherapeutics and insulins can be mentioned.

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The importance of injection depth on the release rate of a drug, especially in the gluteal region, and therefore on the success of the injection therapy, is emphasised in many of the studies reviewed in this article. The relevance excedes however the area of drugs as follows from a recent case report on the i.m. administration of a rabies vaccine (Shill et al., 1987). Despite timely postexposure i.m. vaccine injections in the gluteal region the patient died from rabies encephalitis. The most likely explanation was that the vaccination was placed into the subcutaneous fat. It is also well recognized that injection of hepatitis B vaccine into the gluteal region results in a poorer response than injection into the deltoid muscle. This clinically important aspect of the injection depth has never been discussed in full extent. This article will review the relevant information.

The literature describes many mechanistic speculations on the release kinetics of intramuscular injections mostly based on mathematical diffusion models (Ballard, 1968). A cohesive model, describing the contributing elements and their relative order of magnitude, based on in vivo experiments, especially in humans, and taking into account the aspect of the injection depth, does not exist. This article aims to fill up this gap, focussing on the relation between formulation and physiological factors.

## Injection depth

In 1974 a letter appeared in the Lancet (Dundee et al., 1974) in which the plasma diazepam levels, measured 90 min after i.m. injection of 10 mg diazepam in the buttock were described, depending on the injection technique. All subjects were female. In contrast to the physicians (using a 4 cm needle) most nurses (using a 3 cm needle) injected diazepam too shallowly, in fact in the adipose tissue. The resulting concentrations were much lower in the 3 cm group than in the 4 cm group (Fig. 1).

The authors explained their findings writing that diazepam remains stored in the adipose layers and is absorbed very slowly. The fat layer (subcutis, hypodermis) consists of loose connective tissue

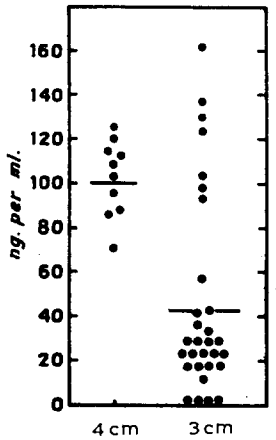


Fig. 1. Plasma diazepam concentrations 90 min after the i.m. injection with a 3-cm or 4-cm needle.

with embedded fat cells. This should then result in much lower concentrations in the plasma.

Many indications can be found in the literature for kinetic differences in drug absorption after intra-adipose (i.a.) or i.m. injection. The following review is subdivided in groups of drugs in aqueous, alcoholic and oily solution and in aqueous and oily suspension. For reasons of clarity the injection in the fat (adipose) layer is further called i.a. injection, according to the suggestion of Morrison (1982), whereas the traditional name intramuscular (i.m.) is used for injections in the muscular tissue.

*Drugs in solution*

The injection depth appears to have an influence on the absorption rate of i.m. (or i.a. respectively) injection aqueous solutions. Examples are cephradine, acetylsalicylate and lidocaine.

The most detailed study was performed on cephradine (Vukovich et al., 1976). The drug was injected into the gluteus maximus, vastus lateralis or deltoid muscle groups, in a randomized crossover study. Smaller areas under the curve, being a measure for the extent of absorption, and smaller absorption rate constants were measured for females after injection into each muscle group (Fig. 2). The phenomenon was most striking when cephradine was injected into the gluteus maximus.

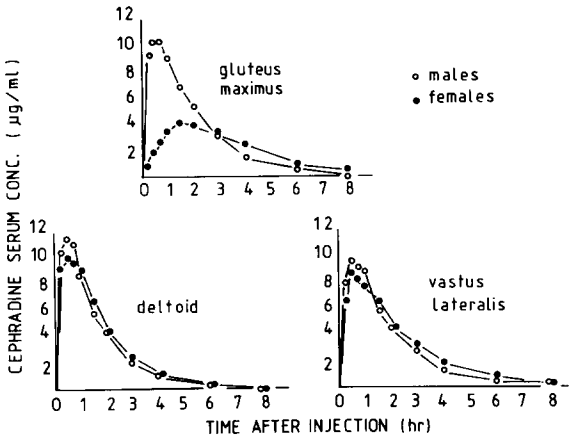


Fig. 2. Cefradine concentrations in serum after i.m. injections of 475 mg in healthy male and female subjects according to site.

The explanation for this sex difference may be that many injections given in the deltoid, and especially in the gluteal region, intended to be i.m. are in fact given in the subcutaneous adipose layer (Modderman et al., 1982; 1983a). It has been found that the depth of gluteal fat is generally more than 3.5 cm, which is the usual length of the injection needle, and that the mean gluteal fat thickness is much greater in women than in men (Cockshott et al., 1982).

Sex differences are also reported for i.m. acetylsalicylate, 1000 mg. It was administered as the lysine salt in an aqueous solution (Aarons et al., 1986). The mean absorption time (MAT) following "i.m." injection appeared significantly longer (97 min) in females than in males (53 min).

I.m. lidocaine was studied in 24 patients, of unknown sex, with suspected myocardial infarction (Zener et al., 1974). A 10% aqueous solution was injected into the deltoid and gluteal muscle on consecutive days. Intradeltoid injection produced higher blood lidocaine concentrations and more rapid development of the peak concentrations than intragluteal injection. The authors conclude that injection into the gluteal area may result in placement of the needle in the adipose tissue, leading to a less rapid absorption.

Diazepam is a lipophilic drug, having a low solubility in water. The diazepam injection is formulated as a solution in a mixture of water and mono- and polyvalent alcohols. Above, the study on i.m. administered diazepam, as given by physicians and nurses respectively, has already been mentioned.

In a study into the bioavailability of oral and i.m. diazepam (Divoll et al., 1983) in a group of 10 males and 12 females it was found that in all the male subjects and in 8 women, absorption of diazepam after deltoid i.m. injection was rapid and essentially complete. However, in 4 subjects, all women, absorption was slower and apparently incomplete.

Kinetic information on i.m. injections of drug solutions in oil is available on medroxyprogesterone acetate (Castegnaro and Sara, 1971) and haloperidol decanoate (Reyntjes et al., 1982). From these studies no conclusions can be drawn on an influence of the injection depth on the release kinetics. They are discussed below in another context.

*Drugs in suspension*

The differences found in absorption rate after i.m. and i.a. injection respectively are not limited to injections of drugs in solution. The differences are even much more pronounced after injection of drugs in suspension. Relevant information concerns procaine penicillin, dapsone and monoacetyldapsone.

In a study on penicillin concentrations, measured in capillary blood, after routine treatment in an out-patient clinic, markedly different concentrations were found in females and males (Juhlin, 1965). The drug was injected i.m. as procaine penicillin in an aqueous suspension in the gluteal region. Concentrations in women were found to be considerably lower than in men.

Dapsone is an important drug for the treatment of leprosy. It is used in a multi-drug treatment (MDT) together with rifampicine and clofazimine, the latter two in monthly administration under supervision (Zuidema et al., 1986). Dapsone has a half-life of about 24 h and must be given daily by self-administration. Patient compliance is a big problem. It is estimated that not more than about 50% of the tablets is actually taken by the patients. This is supposed to be one of the main

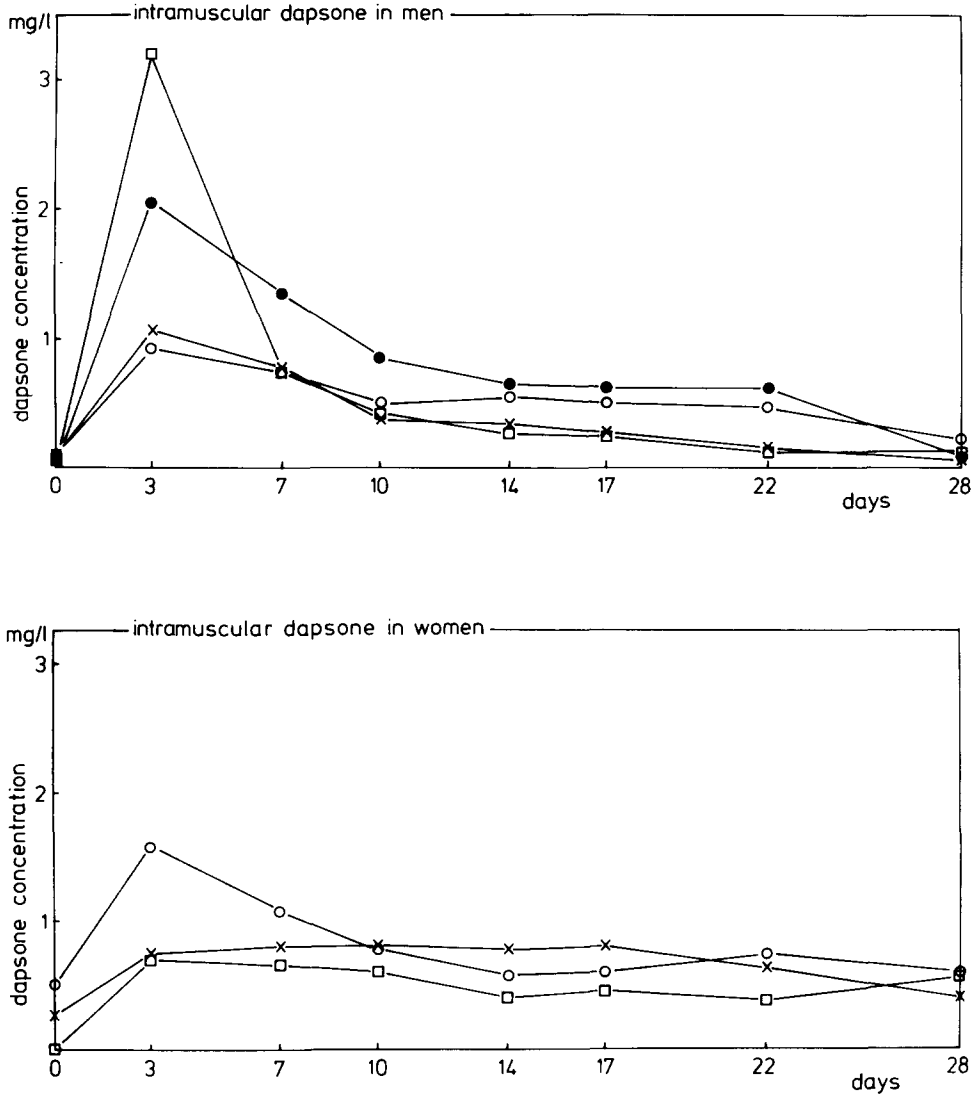


Fig. 3. Some representative dapsone concentration–time curves in serum of a group of 47 males and 30 females given i.m. injections of 900 mg dapsone as an aqueous suspension of double pyramidal crystals, particle size 38–63 μm.

causes of resistance of *Mycobacterium leprae*, the causative agent of leprosy, against dapsone.

Fig. 3 shows the dapsone concentration–time curves in serum in a group of 47 males and 30 females given i.m. injections of 900 mg dapsone as an aqueous suspension of double pyrimidal crystals of a defined size in the gluteus maximus region (Modderman et al., 1983b). It appeared that women have a more sustained absorption than men, resulting in a lower peak concentration in the first week and higher subsequent concentrations over a longer period. It was supposed that in most of the women the injection was actually placed into the adipose tissue.

In view of the above, an i.a. injection in the gluteal s.c. fat layer might eliminate the difference in the time course and this might have advantages in terms of a reproducible and more favourable sustained dapsone appearance in the circulation. Fig. 4 shows the results of a similar dapsone

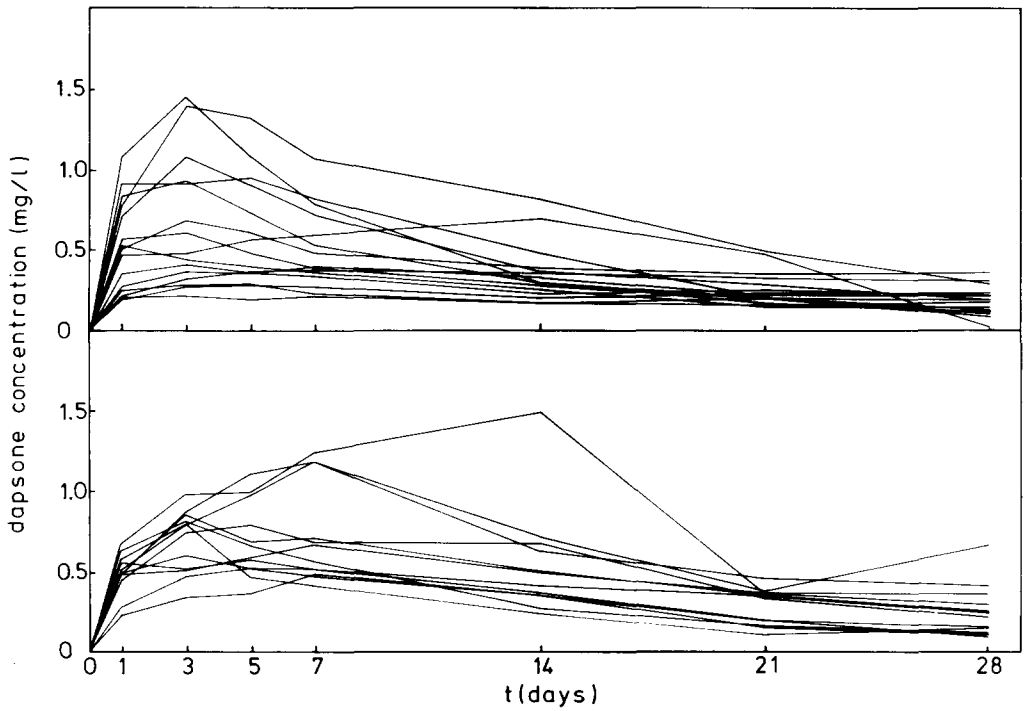


Fig. 4. The dapsone concentration–time curves in serum in a group of 15 males (upper curves) and 12 females (lower curves) given i.a. injections of 1000 mg dapsone as an aqueous suspension of double pyramidal crystals, the particle size being 38–63 $\mu$m.

injection, 1000 mg, given in 15 male and 12 female volunteers at an injection depth corresponding with one-third of the skinfold, being about two-thirds of the gluteal adipose layer (Pieters et al., 1986). As can be seen the sex differences have disappeared completely.

Dapsone is partly acetylated in vivo to monoacetyldapsone. In reverse, monoacetyldapsone can be used as a prodrug of dapsone, since it is partly deacetylated to form dapsone in vivo, resulting in the same equilibrium as after the administration of dapsone. This equilibrium is dependent on the acetylation phenotype of the patient. Monoacetyldapsone is more lipophilic than dapsone and therefore shows a lower dissolution rate and a slower release from its depot.

After the i.m. administration of 700 mg monoacetyldapsone, which corresponds to about 600 mg dapsone, to females and males, the curves appeared to be characterized by a markedly sustained period of drug release of about 2–3 months. Some male volunteers, however, showed peak concentrations in the first 2–3 weeks and a shorter duration of the release.

After the injection of monoacetyldapsone, given at an injection depth of one-third of the skinfold, being about two-thirds of the gluteal adipose layer in 11 male and 11 female volunteers, in a similar way as described for dapsone, the sex differences disappeared completely (Pieters and Zuidema, 1986).

The studies on dapsone and monoacetyldapsone are the first that demonstrate the influence of the injection depth on the release rate, beyond doubt and in a prospective setting.

The mean residence times (MRTs) of the i.m. and i.a. dapsone and monoacetyldapsone injections cannot be calculated exactly, since extrapolation to infinity is not possible. The elimination of dapsone and monoacetyldapsone is characterized by a half-life of about 24 h, corresponding with a mean elimination time (MET) of about 35 h. This is negligibly small in comparison with the estimated MRT, which means that the MATs

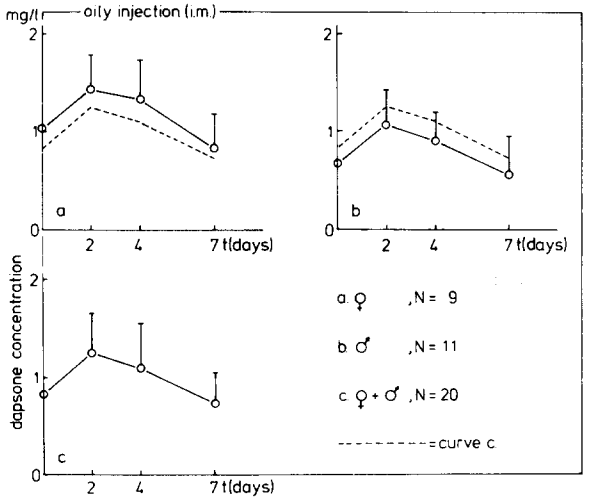


Fig. 5. Dapsone concentrations in serum (in steady state), mean ± S.D., after injection of 375 mg in an oily vehicle (UNICEF injection).

have the same order of magnitude as the MRTs and are in the order of magnitude of weeks and for i.a. monoacetyldapsone even a few months.

Dapsone has also been studied after injection as a suspension in oil. In a trial in 20 Ethiopian leprosy patients 375 mg dapsone was injected i.m. as an oily suspension (UNICEF injections) (Modderman et al., 1983c). The injection is administered weekly. The study suggests that a lower dose frequency is possibly justified. No conclusions or even estimations of the MRT or MAT are possible at the moment.

The sex differences found in this study were small and related to the distribution volume and body weight, respectively; they were not related to the absorption rate (Fig. 5). The study was performed without measuring the thickness of the adipose layer and in a comparable setting as the study on the aqueous dapsone injection (Modderman et al., 1983b) as far as the injection technique is concerned. The study was performed by the same investigators in the same population of patients and at the same time. There are no reasons to suppose that the injection was now not partly administered i.a. It must be concluded that in this case the injection depth had no influence on the release rate.

Suspensions of colloidal drug carriers (liposomes, microspheres, nanocapsules, etc.) have been used to prepare controlled release systems for i.m. use (Arrowsmith et al., 1984; Davis et al., 1987). No information has been described from which the influence of the injection depth on the release can be derived.

## Mechanism of absorption

The release of drugs from an i.m. drug depot appears to be very complicated. From a theoretical point of view some critical steps can be distinguished in the release from an i.m. drug depot: the diffusion of water to the depot, the dissolution step when the drug is in suspension, the diffusion in the dispersing agent, the transfer from the oil to the water phase when the drug is present in an oil phase, the diffusion away from the depot, the distance to the blood system and the blood flow.

In the following sections the rate controlling elements as schematically presented in Fig. 6 are discussed in the sequence of their importance, as expressed by their influence on the mean absorption time, MAT (Table I). The question is whether one or more of these processes have a dominant rate-controlling effect.

*Dissolution rate*

Drugs in suspension, i.m. injected appeared to show MATs of days to weeks, depending on the aqueous solubility of the substance. I.a. injected, the MAT can increase up to several months especially for highly lipophilic drugs with a correlated

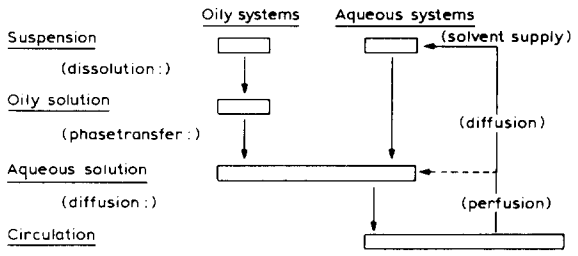


Fig. 6. Schematic representation of the rate-controlling elements in i.m. drug absorption.

TABLE 1

*The order of magnitude of the MAT of suspension or solution injected i.a. or i.m.*

| Type of injection | MAT |
|---|---|
| Aq. suspension, i.a. | weeks–months |
| Aq. suspension, i.m. | weeks(–months) |
| Oily suspension, i.a./i.m. | weeks–months |
| Oily solution lip. drugs i.m./i.a. | hours–month |
| Alc. solution lip. drugs i.m./i.a. | hours |
| Alc. solution lip. drugs i.m. | hour–hours |
| Aq. solution i.a./i.m. | min–hour |

low aqueous solubility such as monoacetyldapsone.

The MAT of drugs in solution, i.m. or i.a. injected, is in the order of magnitude of one or at most a few hours, i.a. slightly higher than i.m.

It appeared that the difference in appearance rate in the circulation from drugs in aqueous or oily solutions is generally small compared with the difference between drugs in solution at one hand and drugs in suspension at the other. This is best demonstrated with medroxyprogesterone acetate which has, after injection in an oil-like system, a kinetic profile similar to that of an oral administration, but which shows a release over weeks after injection as an aqueous suspension (Castegnaro and Sala, 1971).

The suspension state and by consequence the dissolution rate of the drug is obviously the first important rate-controlling element in the release process of the injected suspensions. So it appears from the studies on monoacetyldapsone and dapsone that the release rate of monoacetyldapsone, which has an aqueous solubility an order of magnitude lower, is much smaller than of dapsone.

The dissolution rate of the suspension particles is essentially governed by the Noyes–Whitney law. This law states that the dissolution rate is proportional to the surface area, the diffusion coefficient and the chemical potency, being the concentration gradient. The latter is in its more simple representation the difference between the concentration in the boundary layer, that is the solubility of the compound, and the concentration in the bulk solvent. These factors are the pharmaceutical factors and are easily controlled.

In general the smaller the particle size the larger the surface area and the more rapid the dissolution. Deviations may occur, however, since small particles often tend to aggregate. Aggregation in concentrated systems often gives rise to enlarged viscosities, specific rheological features and a diminished dissolution rate after injection, as is demonstrated on procaine penicillin (Ober et al., 1958).

Altering the suspension medium may change the solubility and by consequence the dissolution rate. It has been found that the addition of 1% benzylalcohol as a preservative to the dapsone injection increased the dissolution and absorption rate dramatically (Modderman and Zuidema, unpublished results).

When the bulk solvent is represented by the blood phase, as often happens, this acts by its large volume as a sink. The Noyes-Whitney law, when simplified for sink conditions, transforms into a zero-order kinetic equation. The decrease of the particle size during the dissolution proces implies however a slowly decreasing release rate, which causes a small deflection of the zero-order equation. The described suspension injections are good illustrations for the validity of such a globally zero-order description.

*Solvent supply and perfusion*

In in vitro flow-through cells, with sufficient water supply, complete dissolution of dapsone and monoacetyldapsone can be achieved in a few hours, whereas the same powders i.m. injected need 1 or 3 months, respectively for complete dissolution (Modderman, 1983). Moreover, it appeared that the difference between dapsone crystals 38-63 $\mu$m and crystals 63-90 $\mu$m was much smaller in vivo than expected from in vitro experiments. This suggests that the solvent, that is the water supply, and in vivo the water diffusion to the depot is also an important rate-controlling element, an element which is controlled by physiological factors. The small water supply, caused by the low degree of vascularisation in the fat layer strongly decreases the release rate of drugs injected in the fat layer.

In physical terms a diminishing solvent supply has to be interpreted as an increasing size of the

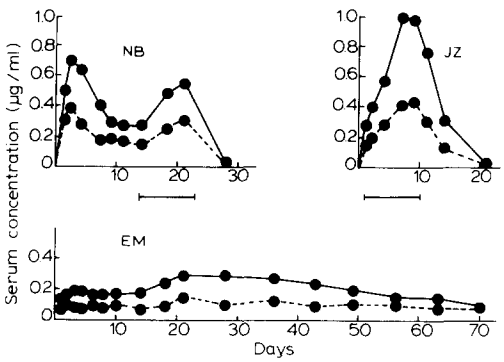


Fig. 7. The influence of an infiltrated abscess in the injected area on the dapsone concentration–time curve in serum after administration of monoacetyldapsone. The duration of the abscess is indicated in two subjects by a horizontal bar. A normal curve (EM) is added for comparison.

unstirred layer, resulting in a decreasing dissolution rate. Theoretically there are two possibilities: the solvent supply is limited by the blood flow or vascularisation, or it is limited by the diffusion from the vascular system to the drug depot. In most of the literature, the first possibility is deemed the most likely.

A convincing illustration of the influence of the perfusion is the lower absorption rate of i.m. gentamicin in patients with spinal cord injury than in controls. The patients showed a reduced muscle blood flow in the paralyzed muscle. The bioavailability remained unaffected (Segal et al., 1986; Segal, 1987).

Another important indication has been found with monoacetyldapsone. After the i.m. and i.a. injections of monoacetyldapsone incidentally infiltrations followed by abscesses have been seen (Pieters et al., 1988). Fig. 7 is a representative dapsone concentration curve in serum in which the abscess period is indicated. During the abscess the release rate is dramatically increased. This may be explained by the higher perfusion of the infiltrated area, the increased local temperature and the related oedema.

Blood flow limitation of the solvent supply implies again that essentially the release process will obey zero-order kinetics.

It is understandable that the gluteal region offers the best contribution to a sustained release (Vukovich et al., 1976; Fig. 2). The adipose layer is thicker in the gluteal region. Moreover, from a study with $^{133}Xe$ it appeared that the resting human muscle blood flow was significantly greater in the deltoid than in the gluteus maximus, the vastus lateralis being intermediate (Evans et al., 1975).

In this context an explanation can be found for the abscence of sex differences of the oily dapsone injection. Independent of the place of the injection, muscle or adipose tissue, the solvent supply, being the oil in this case, is identical. The oil remains rather long the dissolution rate-determining solvent, since the degradation of oil in the depot may need up to several months (Gray, 1978). The unstirred (oil)-layer is independent of the blood flow. Relatively small differences in diffusion time to the vascular system, occurring by variation in injection depth, are not detectable in this setting.

*Phase transfer*

Medroxyprogesterone acetate has been experimentally dissolved in an oil-like system, ethyloleate (Castegnaro and Sala, 1971). In contrast with the commercially available aqueous suspension, which is used as a controlled-release preparation for many weeks, this system shows no substantial retardation of the release. The excretion pattern and rates of the metabolites are essentially the same as after oral administration.

Haloperidol decanoate, dissolved in sesame oil, in contrast shows a sustained release of more than a month (Reyntjes et al., 1982). The curve between dose intervals shows a half-life of about 3 weeks. Since the hydrolysis of the ester, distribution and elimination are fast compared with the absorption, this half-life essentially reflects the absorption rate. The corresponding MAT is estimated to be about one month. This half-life and MAT are in accordance with the accumulation rate found.

Medroxyprogesterone acetate is an ester of a short-chain fatty acid, haloperidol decanoate of a medium chain fatty acid. Esters of the latter type are much more lipophilic. As will appear from the following section the diffusion to the vascular system is correlated with MATs up to only several hours. The difference in MAT is therefore best

explained by the oil-water transfer (distribution coefficient), being the third important rate-determining element.

There is more evidence illustrating the importance of phase transfer as rate-controlling element. Testosterone propionate solutions in different oily solvents have been examined with respect to their release rate in vivo (Al-Hindawi et al., 1987). The disappearance from the injection site appeared rectilinearly related to in vitro partition coefficients. The MATs are estimated to be a few days to about 2 weeks.

These results have been confirmed by a study in rats with solutions of several drugs in several oily liquids (Tanaka et al., 1974). No correlations were found between the viscosity of the vehicle and the absorption rate but there was a distinct relation with the partition coefficients and with the phase transfer rates. Absorption rates were enhanced by the presence of some lipophilic non-ionic surfactants.

Experiments in males show also the influence of non-ionic surfactants on the release rate. The surfactant sorbitan oleate has an increasing influence on the release rate of a $\beta$-lactam antibiotic from an ethyl oleate suspension (Timmins et al., 1986). The effect was explained in terms of reduction in interfacial tension and improved wetting of the powder by the vehicle. The MATs are in the order of magnitude of a few hours.

*Diffusion to the vascular system*

For physicotechnical data on aqueous supensions for injection see to Hirano et al., 1981. Interesting is the conclusion in this study that the influence of low concentrations of viscosity enhancers on the release rate is very small. That means that the diffusion within the dispersing agent is not an important rate-controlling process.

A fourth important contribution, however, to sustained release is made by the diffusion through the adipose layer. Diffusion obeys Fick's laws (Ballard, 1968). This law transforms, after simplification for sink conditions, to a first-order kinetic equation. Diffusion controlled are the more rapidly absorbed drugs in solution. Thus in the related paragraph (2.1.) discussed, injections all are illustrations of the validity of the approximately first-order kinetic absorption model for this kind of formulations.

As is shown the injection in the adipose layer of drug solutions results in a lower release of especially lipophilic, but also hydrophilic drugs, with MATs of one to a few hours. The adipose layer differs from the oil phase of an oily injection by its high viscosity and by its specific histological structure.

*The nature of the retaining bonds*

Studies on the nature of the retaining bonds after i.m. and i.a. injection are lacking in the literature. The lipoidal barriers of the outer skin and alimentary tract have been investigated. Epidermal (stratum corneum) lipids contain predominantly apolar lipids as neutral (60–80% free sterols, long chain fatty acids, triglycerids and highly non-polar species, e.g. *n*-alkanes and squalene), sphingolipids (15–35%) and negligible polar lipids as the phospholipids. Cholesterol sulfate was found in a significant amount in the stratum granulosum (Lampe et al., 1983a; 1983b; Curatolo, 1987). Information concerning the subcutaneous adipose layer is lacking at the moment but it is likely that the lipids have a more polar character since this layer is permeable to water.

A comparison with the different kinds of diffusion through the mucous oral membranes might be explanatory in this context. The keratinized oral epithelium and epidermis shows a pattern of lipid distribution similar to the stratum corneum of the skin. The non-keratinized epithelium, however, contains more polar lipids and few neutral lipids, particularly cholesterol sulfate and glucosylceramides. These regions have a greater permeability, especially to water (Squier et al., 1986). It is likely therefore that the physical retaining elements, lipid solubility and protein binding, are comparable in the non-keratinized mucous membranes and the subcutaneous adipose layer.

The group of the $\beta$-receptor-blocking agents appeared an ideal group for the investigation of the role of hydrophilicity and lipophilicity in drug absorption over mucous membranes and has been investigated after sublingual (s.l.) and vaginal administration. The series propranolol (lipophilic), alprenolol (intermediate) and metoprolol (hydro-

philic) for instance do not differ significantly in $pK_a$, but markedly in lipophilicity. They all are subject to first-pass elimination, which permits the neglect of the gastrointestinal absorption way after swallowing.

It appears that the lipophilic propranolol and the intermediate alprenolol are both rapidly and well absorbed by the oral mucosa, about 3 times more than the oral absorption. The more hydrophilic metoprolol, however, is not absorbed in a significant amount, showing a s.l. bioavailability not different from that after oral administration (Duchateau et al., 1986a and b). The MATs of propranolol and alprenolol after s.l. administration, however, are different, $1.1 \pm 0.3$ and $0.4 \pm 0.2$ respectively, which illustrates a certain depot effect for the more lipophilic propranolol. This has also been found in several other studies (Hicks, 1973; Kates, 1977; Schürmann and Turner, 1978; Henry et al., 1980). A similar phenomenon as found for propranolol is demonstrated for nifedipine (Brown et al., 1986) and morphine (Bell et al., 1985).

Propranolol has also been administered per vaginam where it shows also a slow but good absorption, better than after oral administration, and a clear depot effect (Blumenthal et al., 1977; De Boer et al., 1984).

So it appears that the very hydrophilic drugs are not absorbed after s.l. and vaginal administration, moderately hydrophilic drugs administered in solution are rapidly absorbed, showing a MAT lower than 1 h, whereas more lipophilic drugs, administered in solution, show a depot effect, illustrated by their MAT in the order of magnitude of one to several hours.

A similar relation is likely in i.m. injected drugs but studies in this field have never been carried out. Indications can be derived from the observation of a marked depot effect of the lipophilic diazepam and in a much lower degree of the hydrophilic cephradine after injection in solution (Divoll et al. 1983; Vukovich et al., 1976).

This may be caused by a difference in diffusion rate through the adipose layer, which may behave like a chromatographic system. Moderately hydrophilic substances are transported through the intercellular aqueous media, driven by the concentration gradient, whereas lipophilic substances are retained by absorption and adsorption to the lipid structures.

The influence of surfactants on the diffusion process is not unambiguous. One study describes a promoting effect on the absorption rate of a badly absorbed water soluble antibiotic (Matsuzawa et al., 1969). Several mechanisms have been postulated, such as increased capillary permeability and, more likely, a protection against precipitation. The reverse, retarding effects, has however been reported in more extended studies with a series of polysorbates and a series of water-soluble well absorbed drugs (Timmins et al., 1986, Kobayashi et al., 1974). The relative absorption rate of the drugs appeared more dependent on the surfactant concentration than on the absolute amount of surfactant, which suggests a mechanism related to the formulation rather than related to the transport rate through the extracellular space and connective tissue. Several other mechanisms have been postulated operating alone or in combination. No explanation, however, is completely satisfactory at the moment.

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