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Fundamental understanding of drug absorption from a parenteral oil depot

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ABSTRACT

Oil depots are parenteral drug formulations meant for sustained release of lipophilic compounds. Until now, a comprehensive understanding of the mechanism of drug absorption from oil depots is lacking. The aim of this paper was to fill this gap. A clinical study with healthy volunteers was conducted. An oil depot with nandrolone decanoate and benzyl alcohol was subcutaneously administered in the upper arm of female volunteers. Pharmacokinetic profiles of both substances were related to each other and to literature data. Benzyl alcohol absorbs much more rapidly than nandrolone. In detail, it appears that benzyl alcohol enters the central compartment directly, while nandrolone decanoate is recovered in serum after a lag time. This lag time is also seen in literature data, although not reported explicitly. The absorption of nandrolone is enhanced by the presence of benzyl alcohol. This is most likely an effect of altered oil viscosity and partition coefficient between the oil and aqueous phase. The absorption rate constant of compounds is found to be related to the logP of the solubilized prodrug. The absorption rate is however not only determined by the physico-chemical properties of the formulation but also by the tissue properties. Here, it is argued that lymphatic flow must be considered as a relevant parameter.

1. Introduction

Oily solutions of lipophilic compounds are widely used as a sustained release formulation. Although this pharmaceutical approach has been applied for several decades already, relatively little research has been published on the fundamental parameters that determine the absorption characteristics.

Generally, the formulation of an oil depot contains arachis or sesame oil as well as an amount of benzyl alcohol (BOH) which increases the solubility of the (pro)drug in the oil. In addition to these excipients, the formulation contains the active compound, most often as the esterified substance. Theoretically, there are a number of factors that determine drug absorption from a parenteral oil depot:

1) The drug dissolved in the oil is released as a result of the concentration gradient. Relevant parameters are a) the concentration in the oil, b) the thickness of the diffusion layer as well as the diffusion coefficient in the oil, c) the surface area of the depot, d) the partition coefficient (P) between oil and tissue fluid and finally e) the thickness of the diffusion layer in the aqueous phase as well as the diffusivity in this compartment. Basically, this represents the rate at which the drug is transported through the tissue (Kadir et al., 1990, 1992; Minto et al., 1997; Tanaka et al., 1974; Zuidema et al., 1994, 1988). A simplification of the real vivo situation is depicted in Fig. 1. The oil liquid is not injected directly in the blood stream, while yet the absorption is normally measured in this central compartment (C_{serum}). Therefore, a membrane should be included in this model representing the tissue which is situated in between the oil and the central circulation.
2) BOH exhibits not only a significant solubility in the oil phase, but does also dissolve in the aqueous phase. Consequently, it will also be released out of the depot. Because of the different physico-chemical properties, it can be expected that BOH shows a completely different release profile than the prodrug. BOH in turn has a significant influence on the solubility of the active compound in both the oil and the aqueous phase (Rowe et al., 2009). Therefore, it is obvious that the partition coefficient is not a constant value during the release from the depot. This is presented as the partition coefficient between the concentrations at the interface in Fig. 1.
3) In most cases a lipophilic ester is used as a prodrug. After release out of the oil, this ester has to be hydrolysed to the parent drug. The prodrug exhibits a significantly higher logP than the parent compound. As a consequence, the transport through tissue can be considerably different; highly lipophilic drugs show both retardation by tissue absorption effects and lymphatic transport whereas less lipophilic compounds diffuse directly to the central circulation. Hence, the speed and the place at which (enzymatic) hydrolysis occurs may have impact on the rate of absorption.

Abbreviations: BOH, benzyl alcohol; ND, nandrolone decanoate; P, partition coefficient.

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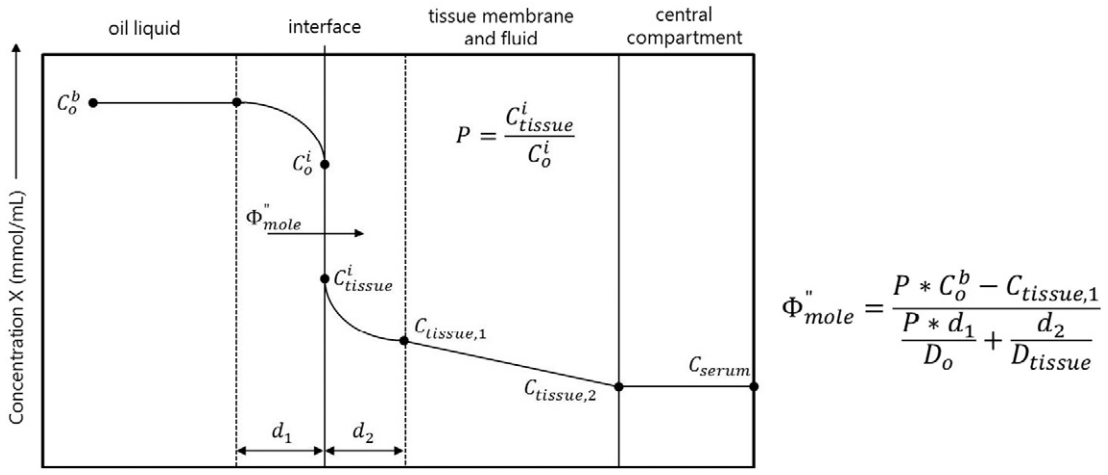

Fig. 1. Schematic overview of the vivo situation (left). Equation on the right presents the parameters which contribute to the mole flux (Φ''_{mole}). Abbreviations: bulk concentration (pro)drug in oil (C_o^b), at oil interface (C_o^i), at tissue interface (C^i_{tissue}), in tissue beginning ($C_{tissue,1}$), before entering central compartment ($C_{tissue,2}$) and in serum (C_{serum}); d = diffusion layer in oil (d_1) and tissue fluid (d_2); P = partition coefficient; D = diffusion coefficient in oil (D_o) and in tissue fluid (D_{tissue}).

Other factors that may also contribute to the absorption rate are: injection depth (Ronald et al., 1993), site of injection (Soni et al., 1988; Vukovich et al., 1975), lymphatic absorption (Zuidema et al., 1994), massage before injection (Soni et al., 1988) and muscle activity (Soni et al., 1988). Although these suggested and obvious factors could lead to a complete understanding of drug absorption from oil depots, no studies have been published on this topic so far. This article makes a distinction between *release* and *absorption* kinetics: substance *release* from the depot can be translated from the mass flux from oil towards the aqueous phase, while *absorption* represents the entire process in which the substance enters in de central compartment. Hence, absorption includes the release out of the oil and the subsequent transfer through the tissue to the blood stream.

The current study started with a clinical trial in which an oil depot containing nandrolone decanoate was used. Frequent sampling of volunteers enabled us to monitor the absorption phase in detail. The aim of this paper is to create further understanding of the fundamental mechanisms that determine the drug absorption from a parenteral oil depot. Second, this paper elucidates the effect of BOH on nandrolone absorption. The observations are compared with results reported in literature and put into perspective with the pharmacokinetic profile of BOH that has been published separately [Kalicharan, BOH article].

2. Materials and methods

2.1. Experimental design

Drug product was manufactured under current Good Manufacturing Practice conditions in the hospital pharmacy at the University Medical Center Utrecht, The Netherlands. Each 1.0 mL of the solution contained 117 μmol nandrolone decanoate (ND), 28,000 IU cholecalciferol, 926 μmol (10% (m/v)) BOH and ad 1.0 mL sesame oil. In this study, 0.5 mL of the solution was subcutaneously (s.c.) injected in the upper arm. Fourteen female volunteers participated in this study. Full informed written consent was obtained from the volunteers, conforming to the Declaration of Helsinki. Inclusion criteria were: good physically and mentally healthy Caucasian females with an age between 65–80 years old and a body mass index (BMI) between 20–30 kg/m^2. Volunteers were excluded when using any drug, food or beverages that influence the metabolism of ND from 2 weeks or 5 half-lives of the medication (whichever is longer) prior to drug administration. Smoking was allowed, provided no more than 4 cigarettes or equivalents were used per day.

A validated LC–MS/MS bioassay was used to determine serum nandrolone concentrations (LoQ = 0.12 pmol/mL). Blood samples were taken directly after injection (0 h) and 2, 4, 8, 12, 15, 22, 24, 36, 48, 72, 96, 168, 216, 264, 360, 456, 552, 648 and 840 h after injection.

2.2. Pharmacokinetic analysis

Pharmacokinetic parameters were examined using Microsoft Excel 2010. The following parameters were determined: maximum serum concentration (C_{max}) and time to reach this concentration (T_{max}); the area under the serum concentration–time curve (AUC) was calculated using the linear trapezoidal rule. All data are expressed as mean ± standard error of the mean (SEM).

2.2.1. Absorption analysis

Drug absorption from the depot was estimated by converting serum levels to total amount of absorbed drug. All serum levels were converted to molar concentrations. The amount of absorption was calculated using the Wagner–Nelson method as described previously (Wagner, 1974). Analysis was performed by the following equation:

$$\frac{A}{V_d} = C_{serum} + k_e * \int_0^t C_{serum} * \mathrm{dt} \quad (1)$$

wherein the maximum (cumulative) amount absorbed into the central compartment equals cumulative amount released by the depot, which was calculated according to

$$\frac{A_{max}}{V_d} = k_e * AUC_{0-\infty} \quad (2)$$

$$AUC_{0-\infty} = \left[\int_0^t C_{serum} * \mathrm{dt}\right] + \frac{C_{serum}^{final}}{\lambda_z} \quad (3)$$

where A and A_{max} are the amount absorbed at moment t and maximal amount absorbed, respectively; C_{serum} and $C_{serum}^{final}$are the serum concentration at time t and the last measured plasma concentration, respectively; λ_z is the apparent elimination rate constant due to flip-flop pharmacokinetics (see below); V_d is the distribution volume and k_e is the elimination rate constant after intravenous injection. Values for k_es in this study were for nandrolone 2.75 h^{-1} (Minto et al., 1997), haloperidol 0.03 h^{-1} (Kudo and Ishizaki, 1999) and testosterone 0.80 h^{-1} (White et al., 1999).