International Journal of Pharmaceutics, 34 (1986) 175–178
Elsevier

IJP 01146

Estimating the maximal potential for intestinal lymphatic transport of lipophilic drug molecules

W.N.A. Charman * and V.J. Stella

Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS 66045 (U.S.A.)

(Received 19 May 1986)
(Modified version received and accepted 3 July 1986)

Key words: Lymphatic delivery; DDT; Chylomicrons; Lipid digestion; Hexachlorobenzene; Oleic acid; Peanut oil

This paper concerns itself with the importance of lipid solubility in a vehicle such as peanut oil (as well as partition coefficient) as an important criteriom for estimating the potential for intestinal lymphatic transport of orally ingested drugs and xenobiotics. Absorbability, and metabolic stability in the lumen and mucosal cells of the molecule, are other important criteria.

The intestinal lymphatic system provides a potential route for drug molecules to enter systemic circulation subsequent to oral administration. The physiology of the intestinal lymphatic system is such that drugs transported from the intestinal lumen by the intestinal lymph gain access directly to the general circulation of the body at the junction of the left internal jugular and left subclavian veins, thereby avoiding initial liver contact (Youmans, 1962). Therefore, the promotion of the intestinal absorption of drug molecules which are susceptible to first-pass liver metabolism may offer a means of circumventing this initial clearance of the drug. In addition, intestinal lymphatic transport of drug molecules affords the possibility of directing the delivery of appropriate agents to various sites of the intestinal and thoracic lymphatic system. There is also the possibility of controlling the rate of entry of molecules into the systemic circulation (Charman and Stella, 1986a).

There is a general belief that the lipophilicity of an administered molecule, as estimated by partition coefficient, e.g. between octanol and water, or between the chylomicron and infranatant phases of lymph, is a major determinant of the eventual degree of lymphatic transport of a lipoidal drug molecule (Sieber et al., 1974; Sieber, 1976; Kamp and Neumann, 1975). This hypothesis is based on the fact that most drug molecules which are transported in significant quantities by intestinal lymph are highly lipophilic, and reside in the chylomicron fraction (as opposed to the infranatant fraction) of intestinal lymph (Sieber, 1976; Kamp and Neumann, 1975; Vost and Maclean, 1984). Chylomicrons are the major lipid-transporting lipoproteins of intestinal lymph, and are composed of a triglyceride core which is stabilized in the aqueous environment of the lymph by a surface coating of protein and phospholipid (Sabesin, 1976; Zilversmit, 1978). An apparent relationship between the partition coefficient of a drug molecule and its lymphatic transport has been demon-

* *Present address*: Sterling-Winthrop Research Institute, Rensselaer, NY 12144, U.S.A.
Correspondence: V.J. Stella, Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS 66045, U.S.A.

strated within a homologous series for a number of DDT analogs (Sieber, 1976) and a series of testosterone esters (Noguchi et al., 1985a).

The importance of partition coefficient from a purely mass transport perspective can be readily seen when chylomicron flow and portal blood flow are compared. Portal blood flow to intestinal lymph flow in the rat is approximately 500 : 1. However, it is the chylomicron flux, and not the volumetric flow of lymph which is important for the transport of lipophilic drugs. Although chylomicron formation is phasic and dependent upon co-administration of absorbable lipids, for illustrative purposes, it will be assumed that the concentration of chylomicron lipid is $\approx 1\%$ of intestinal lymph after ingestion of a long chain fatty acid lipid (Shiau et al., 1985; Tso et al., 1982; Charman et al., 1986a and b). For a drug, completely absorbed from the gastrointestinal tract and metabolically stable in the lumen and intestinal cells, to be transported to equal extents by the portal blood and the intestinal lymph, on flow considerations alone, the molecule would require a partition coefficient of at least 50,000 in favor of chylomicron lipid (and not 1-octanol). The logarithm of this value is 4.7, which is consistent with the minimal partition coefficient values which Noguchi et al. (1985a) have suggested are required for significant lymphatic transport.

As most lymphatically transported lipophilic drugs are present in the chylomicron fraction of intestinal lymph, there are two major factors which can influence the amount of drug transported by this intestinal absorptive pathway. Firstly, the quantity of lipid transported in the lymph in the form of chylomicrons and secondly, the amount of drug per chylomicron. From a pharmaceutical viewpoint, both of these factors can be manipulated (to some extent) in order to optimize and/or promote the lymphatic transport of particular drugs. The chylomicron flux can be influenced by factors such as the type of lipid vehicle which is co-administered with the drug and diet. The loading of drug per chylomicron will be affected by a combination of partition coefficient and lipid solubility considerations (which can potentially be manipulated through analog and prodrug development), as well as the class of lipid vehicle in which the drug is administered (Charman and Stella, 1986a).

Measurements of partition coefficient and lipid solubility are often utilized as estimates of the lipophilicity of a particular molecule. The partition coefficient is the ratio of the equilibrium solution partitioning of a drug between an organic and an aqueous phase (often, 1-octanol and water). Lipid solubility is an absolute measurement of the solubility of a solute, in equilibrium with its solid phase. It is possible for a compound to have a large log P value but not necessarily a high solubility in a lipid such as a triglyceride while another compound may be very soluble or even miscible with triglyceride but have a relatively low log P value. In addition, a high solubility of a compound in a solvent such as 1-octanol or chloroform will not always relate to a high solubility in a poorly solvating, largely hydrocarbon vehicle such as a long chain fatty acid triglyceride.

It has been reported that the dose volume of particular lipids had no significant effect on the intestinal lymphatic transport of benzo(a)pyrene (50 μmol and 500 μmol of olive oil, Laher et al., 1984) and DDT (50 μl and 200 μl of various lipids; Charman and Stella, 1986a). Although there was no effect of dose volume on the cumulative lymphatic transport of DDT, the concentration of DDT per chylomicron was proportionally higher when administered in the 50 μl than in the 200 μl dose volume (Charman and Stella, 1986a). These observations suggest that the lymphatic transport of a lipophilic compound, via chylomicrons, may eventually be limited by the solubility of the drug in the triglyceride core of the chylomicron.

To partially evaluate the effect of lipid solubility of a lipophilic molecule on intestinal lymphatic transport, two model compounds (DDT; 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethane; and HCB, hexachlorobenzene) with differing lipid solubilities, but similar partition coefficients, were administered to mesenteric cannulated animals and their lymphatic transport measured. DDT and HCB have similar octanol/water partition coefficients ($\log P_{o/w}(DDT) = 6.19$ and $\log P_{o/w}(HCB) = 6.53$, Patton et al., 1984) although their solubilities in peanut oil differ by more than an order of magnitude (Table 1). In addition, both com-

TABLE 1

EQUILIBRIUM SOLUBILITIES OF DDT AND HCB IN PEANUT OIL AT 25°C AND THE RESPECTIVE INTESTINAL LYMPHATIC TRANSPORT OF THESE COMPOUNDS (0–10 h POST-DOSING) IN RATS

Compound [a]	log(partition coefficient) [b]	Lipid solubility [c] (g solute/100 ml lipid)	Cumulative lymphatic transport (0–10 h, % dose [d])
DDT	6.19	9.75 ± 0.15	33.5 ± 2.3
HCB	6.53	0.75 ± 0.05	2.3 ± 0.05

[a] DDT and HCB (Aldrich Chemicals, Milwaukee, U.S.A.) were of greater than 99% purity as determined by Differential Scanning Calorimetry.

[b] Octanol/water partition coefficients, from Patton et al. (1984).

[c] Equilibrium solubilities at 25 ± 0.5°C, in peanut oil, determined by HPLC analysis. Mean ± S.D. for $n = 3$ determinations.

[d] Cumulative % dose lymphatic transport in the 0-10 h post dosing period. Mean ± S.E. for $n \geq 4$ determinations. DDT was given at 10 mg/200 μl of oleic acid and HCB was administered at 1 mg/200 μl of oleic acid.

pounds are relatively metabolically stable in rat tissues and are not degraded within the intestinal lumen or mucosal cells. The lymphatic transport of DDT and HCB was followed by HPLC analysis of lymph samples by a previously described method (Noguchi et al., 1985b).

Both compounds were administered intraduodenally, dissolved in 200 μl of oleic acid, by a 2 h infusion. For details of the procedure, refer to Charman et al. (1986b). Both compounds were administered at approximately 60% of their saturated solubility (in an equivalent volume of peanut oil) in an attempt to keep the thermodynamic activity of both compounds at equivalent levels. Oleic acid (fatty acid) rather than peanut oil was used as the lipid vehicle in these experiments. This was done to overcome the need for preabsorptive hydrolysis which a triglyceride vehicle would need to undergo before absorption by the enterocyte. In addition, lymphatic transport of DDT has been shown to be greater when administered in an oleic acid vehicle as opposed to a triglyceride vehicle (Charman and Stella, 1986a). Oleic acid is not transported in the lymph per se. It is utilized in the enterocytes in the resynthesis of the corresponding triglyceride, which then forms the core material of the chylomicron. Solubilities of DDT in peanut oil have been utilized as a model for the solubility of DDT in the triglyceride core of the chylomicrons, as oleic acid is the major fatty acid of peanut oil (Windholz and Budavari, 1983).

Table 1 describes the intestinal lymphatic transport of DDT and HCB in rats, and their respective equilibrium lipid solubilities in peanut oil at 25°C. Most notable is the close parallel between the cumulative 10 h lymphatic transport of these two model compounds (% dose DDT transported/% dose HCB transported = 14.6) and their solubilities in peanut oil (DDT solubility/HCB solubility = 13.0). This data indicates the importance of lipid solubility in determining the ultimate lymphatic transport of drugs with high partition coefficients.

Notwithstanding the importance of lipid solubility for lymphatic transport, the partition coefficient of the molecule is a critical parameter as it describes the relative affinity of a drug for either the lipoidal (lymphatic route) or aqueous environments of the enterocytes (Vetter et al., 1985) and portal blood. However, a potential problem with the use of partition coefficient as the sole indicator of the potential lymphatic transport of a drug is that it is a relative measurement and not an absolute quantity, as is the solubility of a drug in a triglyceride solvent.

If asked the question, "will drug X, with a log P value > 5 (1-octanol/water), be transported via the intestinal lymphatics after oral administration" it should be possible to predict the *maximal* possible amount of drug transported. If drug X is administered in a lipid vehicle, such as a long chain fatty acid, monoglyceride, or triglyceride, capable of promoting chylomicron formation, or is administered after a fatty meal, it is reasonable to assume that ≈ 50% of the lipid will be con-

verted to a triglyceride in the enterocytes and ultimately appear as the core component of chylomicrons in intestinal lymph (Tso et al., 1982; Charman and Stella, 1986a). For DDT, the loading of drug per chylomicron triglyceride is as high as 0.6–2% by weight (Vost and Maclean, 1984; Charman and Stella, 1986a). These values are approximately 6–20% of the saturated solubility of DDT in a triglyceride. Since a drug is unlikely to be present at > 25% of its saturated solubility in chylomicrons, knowing the solubility of drug X in a triglyceride like peanut oil will allow one to predict the maximal likely concentration of drug X in chylomicrons. The product of the estimate of maximal drug X concentration in chylomicrons (25% of saturation) and the volume of lipid transported gives an estimate of the maximal likely amount of drug X transported via the intestinal lymphatics. The solubility of drug X in a vehicle such as peanut oil compared to the likely administered dose will provide a quick reference point on the likelihood of achieving significant lymphatic delivery of that agent. It should be remembered that the drug must also have a log P value of 5–6 and the actual amount transported is likely to be less than the estimated value if the drug is subject to lumenal or mucosal cell metabolism or is incompletely absorbed.

In summary, the potential for intestinal lymphatic transport of a drug can be estimated after consideration of lipid solubility in a vehicle like peanut oil, its partition coefficient and chylomicron transport. The partition coefficient describes the relative affinity of the administered drug for enterocyte oil globules (pre-chylomicrons; Vetter et al., 1985) and chylomicrons relative to the enterocyte cytosol and portal blood. The solubility of the administered drug in triglyceride represents the capability, and subsequently the limits, of the lymphatic system for the transport of lipophilic drugs.

Acknowledgements

This work was supported by R.P. Scherer Corporation. The authors wish to thank Dr. T. Noguchi for helpful discussions and Mr. S. Kundu for performing the solubility studies.

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