International Journal of Pharmaceutics, 33 (1986) 165–172
Elsevier

IJP 01115

Effects of lipid class and lipid vehicle volume on the intestinal lymphatic transport of DDT

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

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

(Received 21 October 1985)
(Modified version received 23 May 1986)
(Accepted 27 May 1986)

Key words: Lymphatic transport – Vehicle effects – Vehicle volume – DDT

Summary

The effect of lipid vehicle volume and lipid class on the intestinal lymphatic transport of DDT (1,1-bis(*p*-chlorophenyl)-2,2,2-trichlorethane; *p,p*-DDT) has been investigated in anesthetized rats. Two milligrams of DDT, dissolved in either 50 μl or 200 μl of lipid, was infused intraduodenally. The lymphatic transport of DDT was followed by HPLC analysis of hourly lymph samples collected from the intestinal mesenteric lymph duct. Three types of lipid vehicles were utilized in this study, peanut oil (triglyceride), oleic acid (fatty acid) and a 2 : 1 mixture of oleic acid–monoolein, which represents the lumenal digestion products of a triglyceride. There were major and significant differences in the kinetics of lymphatic transport of DDT and in the cumulative amount of DDT transported when administered in the different lipid vehicles. Cumulative intestinal lymphatic transport of DDT was greatest when administered in either oleic acid or the 2 : 1 mixture of oleic acid–monoolein. Peanut oil was the least effective lipid vehicle with respect to the lymphatic transport of DDT. A comparison of the lymphatic transport of DDT when administered in the two dose volumes revealed no significant difference in the cumulative transport of DDT within a particular lipid class (triglyceride, fatty acid or oleic acid-monoolein).

Introduction

The intestinal lymphatic transport of lipophilic compounds appears to be associated with concurrent lipoprotein synthesis by the enterocytes of the small intestine. Lipophilic molecules which are transported to a significant extent by the intestinal lymphatic system are either solubilized by, or associated with, the triglyceride core of chylomicrons which are the major triglyceride transporting lipoproteins of the small intestine (Sieber, 1976; Vost and Maclean, 1984; Charman et al., 1986). Although chylomicron formation is a complex process (Sabesin, 1976; Zilvermist, 1978), it is known that long chain fatty acids, or their triglyceride equivalent, are essential for their formation. It is for this reason that lymphatically absorbed lipophilic drugs are best co-administered with a lipid vehicle comprised of long chain fatty acids. Not all fatty acids promote chylomicron formation. Short and medium chain fatty acids are absorbed to a greater extent by the portal blood rather than the lymphatic system and subsequently are not substrates for chylomicron tri-

* *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.

glyceride formation. The degree of unsaturation of the fatty acids in the administered lipid can also affect the relative blood and lymph absorption profiles of the fatty acid (Ockner et al., 1972; McDonald et al., 1980).

Numerous reports appear in the literature concerning the lymphatic transport of lipophilic drugs (Kamp and Neuman, 1975; Ueda et al., 1983; Palin et al., 1982; Blomhoff et al., 1984; Laher et al., 1984; Grimus and Schuster, 1984; Noguchi et al., 1985a) co-administered in various volumes of different lipid vehicles. Consequently, it is difficult to evaluate data and extrapolate conclusions among these different studies.

The current studies have been designed to investigate: (a) the effect of lipid class on the lymphatic transport of a model compound; and (b) the effect of co-administered lipid volume on the lymphatic transport of equivalent doses of DDT. DDT has been used as a model compound for these studies for reasons previously described (Noguchi et al., 1985b).

Materials and Methods

Chemicals

The sources of chemicals used in this study were identical to those described earlier (Charman et al., 1986) except for monololein (Fluka AG, Buchs, Switzerland). The monoolein was purified by silica gel column chromatography (E. Merck, Darmstadt) and eluted with hexane-diethyl ether (60 : 40). Separation was followed by thin-layer chromatography as described by Christie (1973). Diethyl ether was used after glass distillation. All other chemicals were of analytical grade.

Animals and surgical procedures

Male Sprague–Dawley rats (250–300 g) were purchased, handled, and housed as described in detail earlier (Charman et al., 1986) as were the lymphatic transport studies, including surgical procedures for mesenteric lymph duct cannulations (Noguchi et al., 1985b). For the unabsorbed DDT studies, the jejunum was cannulated 20 cm below the Ligament of Treitz with 0.4 cm and lipid. The bile duct was not cannulated and was assumed to be free flowing in these experiments.

Drug administration

After a 24 h period of fasting, animals ($n = 4$) underwent sequential tracheal, intestinal lymphatic and duodenal cannulation. Animals were maintained under constant anesthesia by 2 hourly intraperitoneal injections of 50 mg/kg pentobarbitone sodium (D-M Pharmaceuticals, Sellersville, PA 18960, U.S.A.). After surgical procedures were completed, rats were secured on a heated pad (Clinical Scientific Equipment, Melrose Park, IL 60160, U.S.A.) maintained at 37°C. An intraduodenal infusion of normal saline containing 0.2% Tween 80 at 1.44 ml/h, via an infusion pump (Sage Instruments, Cambridge, MA 02139, U.S.A.) was subsequently begun which maintained body hydration and intestinal lymph flow. Three hours later, 2 mg DDT dissolved in either 50 μl or 200 μl of a lipid vehicle (containing no Tween 80) was infused, by a second infusion pump, over a 2 h period via a T-piece connector (Technicon Instruments Corporation, Tarrytown, NY 10591, U.S.A.) into the flowing stream of normal saline–Tween 80 solution. For a detailed description of these procedures, please refer to Charman et al. (1986).

Immediately after starting the lipid infusion, lymph was collected hourly into collection tubes (10.25 mm × 50 mm; Terumo Medical Corporation, Elkton, MD 21921, U.S.A.) containing 3 mg EDTA dissolved in 200 μl normal saline solution. The EDTA solution inhibited clot formation in the collected lymph. Following the 11–12 h experimental period, the animals were sacrificed by sodium pentobarbital overdose, the abdomen opened, and the integrity of all cannula verified.

Intestinal recovery of intraduodenally administered DDT

Rats ($n = 4$) were fasted for 24 h prior to cannulation of the trachea, duodenum and the jejunum as described. The intestinal lymphatics were not cannulated in these experiments. Under constant anesthesia, animals underwent identical administration of DDT and associated lipid vehicle

as those in which the mesenteric lymph duct was cannulated. At 5 h post-dosing initiation (2 h drug infusion plus 3 h normal saline infusion), the intestine, from the point of duodenal cannulation to the glass tubing implanted in the jejunum, was rinsed with 40 ml of normal saline–Tween 80 solution. Testosterone undecanoate was added as an internal standard and the collected washings were extracted with 100 ml of diethyl ether. A 10 ml aliquot of the organic layer was evaporated to dryness and reconstituted with 600 μl of 5% sodium chloride solution and 300 μl of cyclopentanone. An aliquot of the cyclopentanone solution was then subjected to HPLC analysis and the DDT levels quantitated.

Sample analysis

Quantitation of DDT in hourly lymph samples, and the spectrophotometric estimation of lymph lipid levels were performed as previously described (Charman et al., 1986).

Statistical analysis

Statistical equivalence of group mean values was tested by analysis of variance. If differences were evident at the 95% confidence level, Tukey's pairwise comparison of means was performed.

Results and Discussion

200 μl dose volume

Fig. 1 describes the cumulative % dose of DDT transported in intestinal lymph over a 12 h collection period. The dose volume of lipid in these studies was 200 μl (containing 2 mg of DDT) and was infused intraduodenally over a 2 h period. There were no significant differences in intestinal lymphatic DDT transport when administered in either the oleic acid or oleic acid-monoolein vehicles ($P > 0.05$). In addition, the kinetics of DDT appearance, as indicated by lag-time and rate of transport, were similar. In contrast, when DDT was administered in peanut oil, the rate of transport, and lag-time for DDT appearance in lymph, were qualitatively different from the other two vehicles. Also, the cumulative 12 h lymphatic transport of DDT was significantly different ($P <$ 0.05) to that observed from the fatty acid vehicles.

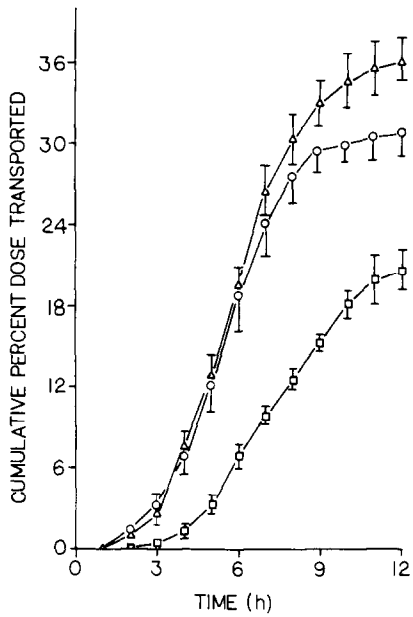


Fig. 1. Cumulative percent dose of DDT (mean ± S.E., $n = 4$) collected in intestinal lymph as a function of time and lipid vehicle. Dose of DDT was 2 mg dissolved in 200 μl of administered lipid. Infusion period was 2 h. △———△, oleic acid; ○———○, oleic acid–monoolein (2:1); □———□, peanut oil.

The apparent quantities of lipid transported in the intestinal lymph over the collection period were not significantly different when comparing the three lipid vehicles, as indicated in Table 1. These values were calculated indirectly from cumulative optical density measurements of diluted lymph samples, as described by Charman et al. (1986). Therefore, the differences in lymphatic transport of DDT when administered in these three different lipid vehicles does not appear to be a direct function of differing degrees of total lymph lipid transport.

Lymph lipid transport is an important factor in determining the lymphatic transport of DDT. Chylomicrons are lipoproteins that have a major role in lipid transport and the lymphatic transport of DDT appears to be associated with this process (Sieber, 1976; Vost and Maclean, 1984; Charman et al., 1986). Charman et al. (1986) demonstrated that the relationship between the hourly transport

TABLE 1

APPARENT QUANTITIES OF LIPID TRANSPORTED IN INTESTINAL LYMPH AND CUMULATIVE VOLUMES OF LYMPH COLLECTED IN THE 12 h POST-DOSING PERIOD WHEN DDT WAS ADMINISTERED IN DIFFERING LIPID VEHICLES

Lipid vehicle containing 2 mg DDT (Infusion period was 2 h)	Cumulative lymph volume (0–12 h) [a] (ml)	Apparent quantity of lymph lipid transported [a,b] (0–12 h)
200 μl peanut oil	5.99 ± 0.65	76 ± 4.4 mg [d]
200 μl OA-MG [c]	4.68 ± 0.40	89 ± 4.3 mg [d]
200 μl oleic acid	6.57 ± 1.03	83 ± 5.4 mg [d]

[a] Mean ± S.E. for at least 4 individual determinations.
[b] Estimated by cumulative OD_{560} measurements. (For details see methods, and Charman et al., 1986).
[c] Oleic acid–monoglyceride (2:1) mixture.
[d] None of the amounts were statistically different from each other.

of DDT and the corresponding hourly chylomicron transport was linear. The slope of the lines describing these relationships represent the relative concentration, or loading, of DDT per unit of chylomicron lipid. The regression equations, with appropriate statistics, describing the relationship between hourly lymphatic DDT transport (μg/h) and chylomicron (CM) transport as indicated by optical density measurements (OD/h) for the three lipid vehicles studied here are as follows: oleic acid, DDT (μg/h) = 1.49 + 5.43 CM (OD/h), $n = 42$, $r = 0.9727$; oleic acid–monoolein, DDT (μg/h) = −10.32 + 5.45 CM (OD/h), $n = 42$, $r = 0.9732$; and peanut oil, DDT (μg/h) = 4.61 + 2.68 CM (OD/h), $n = 41$, $r = 0.8892$.

The differences in the slopes of the regression lines, indicative of DDT loading per chylomicron lipid, are consistent with the differences in cumulative lymph transport of DDT when administered in the three different lipid vehicles, i.e. since there is apparently similar lipid transport, the ratio of the apparent loading of DDT per chylomicron between any two lipid vehicles (as estimated by the slope of the regression lines) reflects the ratio of total DDT transport over the 12 h post-dosing initiation period when administered in the same two lipid vehicles. Potential reasons for the different apparent loadings of DDT will be discussed later.

Lymph flow over the 12 h post-dosing period is described in Fig. 2. Although chylomicron flow rather than lymph flow appears to be the major determinant of lymphatic DDT transport (Charman et al., 1986), these data confirm no significant or unusual effects of the three lipid vehicles on the flow of lymph during the lymph collection period.

Additional experiments were performed to estimate the quantity of unabsorbed DDT present in the intestinal lumen after intraduodenal administration in the different lipid vehicles. The site of intestinal collection of unabsorbed DDT was the proximal ileum, which is distal to the duodenum and upper jejunum where significant lymphatic transport and chylomicron formation occurs (Borgstrom et al., 1957). Therefore, the possibility of decreasing the potential lymphatic transport of DDT by cannulating the intestine at a point too close to the stomach, which could lead to an increase in the quantity of DDT recovered from the intestine, was excluded. There were approximately equal quantities of DDT recovered from the intestinal lumen, 5 h post-dosing when administered in either the peanut oil or oleic acid vehicles, as listed in Table 2. Therefore, the differences in cumulative % dose of DDT transported lymphatically does not appear to be a function of differing degrees of DDT absorbed from the small intestine. The quantity of administered DDT un-

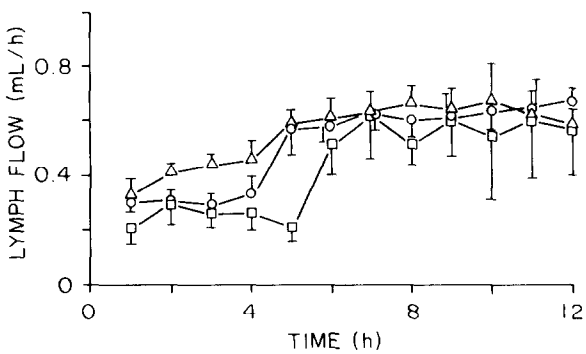


Fig. 2. Hourly lymph flow (mean + S.E., $n = 4$) as a function of time for the three different lipid vehicles. Dose volume was 200 μl containing 2 mg DDT. △——△, oleic acid; ○——○, oleic acid-monoolein; □——□, peanut oil.

TABLE 2

INTESTINAL RECOVERY OF INTRADUODENALLY ADMINISTERED DDT [a]

Lipid vehicle administered	% dose of DDT recovered [b]
Peanut oil	19.6 ± 2.4
Oleic acid	17.6 ± 1.5

[a] Collection made at 5 h post-dosing. Dose was 2 mg DDT/200 μl lipid.

[b] Mean ± S.E. for four determinations.

accounted for after lymph and intestinal washings collection was probably that amount absorbed via the portal blood, or retained by the intestinal cells. The total gastrointestinal absorption of the 2 mg DDT dose appeared to be approximately 80%, with the lymph, and presumably the portal blood, accounting for differing amounts of absorption depending upon the lipid vehicle administered.

50 μl dose volume

In order to investigate the effect of dose volume of lipid on the intestinal lymphatic transport of DDT, similar experiments to those described above were performed with the dose volume lowered to 50 μl of lipid. Fig. 3 describes the cumulative % dose of DDT transported in intestinal lymph over the 11 h post-dosing period. Most notable is the lack of effect that the dose volume of lipid (50 or 200 μl) had on the extent, rate, and lag-time of lymphatic transport of DDT (Fig. 3). At the 50 μl dose volume, the peanut oil vehicle produced the lowest degree of lymphatic transport of DDT, with the oleic acid and oleic acid–monoolein vehicles producing a significantly greater ($P < 0.05$) lymphatic transport. Again, this is consistent with the 200 μl dose volume data in Fig. 1. There was no apparent lag-time for the lymphatic transport of DDT when administered in the oleic acid–monoolein vehicle. The lag time for lymphatic transport of DDT from the oleic acid vehicle was intermediate between the lag-times from the oleic acid/monoglyceride and peanut oil vehicles.

Although attempted, it was not possible to gravimetrically quantitate lymph lipid transport after administration of the 50 μl of lipid because

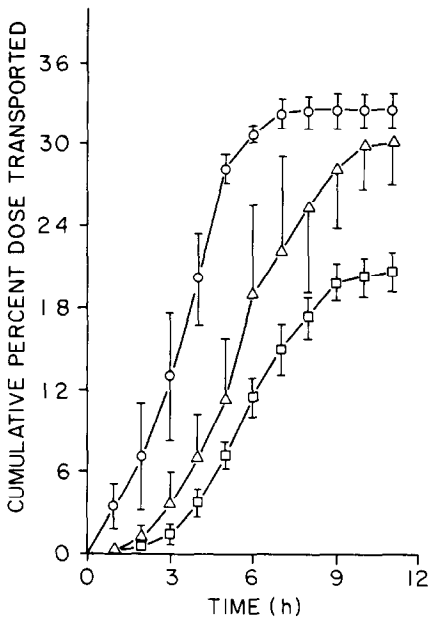


Fig. 3. Cumulative percent dose of DDT (mean ± S.E., $n = 4$) collected in intestinal lymph as a function of time and lipid vehicle. Dose of DDT was 2 mg dissolved in 50 μl of administered lipid. Infusion period was 2 h. △——△, oleic acid; ○——○, oleic acid–monoolein (2:1), □——□, peanut oil.

of insufficient sensitivity. However, there was still a very good correlation between lymphatic DDT transport and the optical density at 560 nm of diluted lymph samples, analogous to the 200 μl dose study. The regression equations, with appropriate statistics, describing the relationship between hourly lymphatic DDT transport (μg/h) and chylomicron (CM) transport as indicated by optical density measurements (OD/h) for the three lipid vehicles were as follows: oleic acid, DDT (μg/h) = −21.5 + 23.95 CM (OD/h), $n = 42$, $r = 0.9545$; oleic acid/monoolein, DDT (μg/h) = −11.4 + 18.21 CM (OD/h), $n = 29$, $r = 0.9750$; peanut oil, DDT (μg/h) = −12.5 + 15.46 CM (OD/h), $n = 41$, $r = 0.9572$.

The negative intercepts in these equations indicate the appearance of particles in the lymph (potentially chylomicrons and/or other intestinal lipoproteins) which did not contain DDT. This may be a function of differential absorption rates

of DDT and lipid from the intestinal lumen into the intestinal cells, or to a differential rate of cellular processing of absorbed DDT and lipid prior to appearance in the lymph. Consistent with the 200 μl volume study, the apparent loading of DDT per chylomicron lipid, as indicated by the slopes of the regression equations, reflect the % dose of DDT transported in the intestinal lymph.

The apparent loading, or concentration, of DDT in the chylomicron lipid is higher when administered in the 50 μl dose volume than when administered in the 200 μl dose volume. The loading of DDT in the chylomicron was approximately 0.5 – 2% by weight, calculated by dividing the recovered quantity of DDT by the amount (by weight) of lipid transported. This number is in good agreement with a report by Vost and Maclean (1984). The solubility of DDT in triolein (a triglyceride which would be similar to that found in the core of a chylomicron) is approximately 8% by weight (Patton et al., 1984). Therefore DDT is present at about 6–20% of its saturated solubility in a long chain triglyceride. This is a good indication of how efficient DDT transport by chylomicron can be under relatively optimal conditions.

Fig. 4 describes the flow of lymph in the post dosing period when DDT was administered in 50 μl of the different lipid vehicles. These data suggest no substantial effect of the lipid class on lymph flow, consistent with the observations made with the 200 μl lipid volumes.

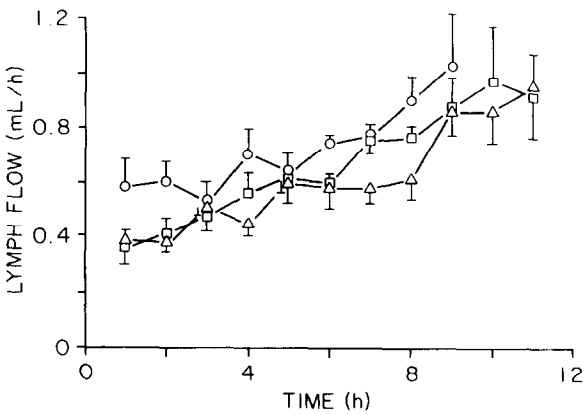
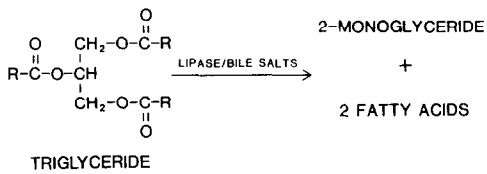


Fig. 4. Hourly lymph flow (mean ± S.E., $n = 4$) as a function of time for the three different lipid vehicles. Dose volume was 50 μl containing 2 mg DDT. △———△, oleic acid; ○———○, oleic acid–monoolein; □———□, peanut oil.

Lipid absorption and lymphatic transport

Inherent in the results just presented, is an evaluation of the potential effect that the initial hydrolysis of a triglyceride in the lumen of the small intestine has on the eventual lymphatic absorption and transport of DDT. Scheme 1 depicts



Scheme 1

the reaction scheme for the preabsorptive hydrolysis of a triglyceride molecule in the lumen of the small intestine. Pancreatic lipase catalyzes the hydrolysis of a triglyceride and the resulting fatty acid–monoglyceride products are solubilized in bile salt/lecithin micelles prior to passage into the enterocyte. Fatty acids and monoglycerides can be absorbed directly by the enterocyte whereas a triglyceride molecule must be hydrolyzed prior to absorption (Vetter et al., 1985).

The three lipid vehicles used in the present study represent some of the possible lipoidal phases resulting from lumenal lipid digestion. The peanut oil (triglyceride), oleic acid (fatty acid) and 2 : 1 mixture of oleic acid–monoolein [1] are essentially fatty acid equivalent, as oleic acid is the major fatty acid constituent of peanut oil (Windholz and Budavari, 1983).

[1] The monoglyceride isomer used in this study was the thermodynamically more stable 1-monoglyceride, as opposed to the 2-monoglyceride. During triglyceride digestion, the 2-monoglyceride is the major isomer produced although subsequent isomerization does occur. Therefore, although the monoglyceride–oleic acid vehicle is referred to as a synthetic digestion mixture of a triglyceride, in terms of a strict definition, it does not represent the immediate products of lumenal triglyceride hydrolysis. The consequences of using the 1-monoglyceride, rather than the 2-monoglyceride, are unknown.

Kinetics and dynamics of lymphatic absorption of DDT and lipic vehicles

There is no apparent effect of dose volume (50 or 200 μl) of the same lipid vehicle on the lymphatic transport of DDT. These data confirm, and extend, the observations of Laher et al. (1984) who studied the intestinal lymphatic transport of benzo(a)pyrene in the rat after administration in either 50 or 500 μmoles of olive oil.

There is, however, an effect of the administered lipid vehicle on the lymphatic transport of DDT. The oleic acid and oleic acid–monoolein vehicles produced greater lymphatic transport of DDT than the corresponding fatty acid equivalent triglyceride at either the 50 μl or 200 μl dose volumes.

There are many potential reasons for the apparent lipid vehicle effect of the fatty acid equivalent triglyceride and fatty acid lipid vehicles on the lymphatic transport of DDT. The effect does appear to be related to the initial hydrolysis that a triglyceride must undergo prior to absorption. The longer lag-time prior to lymphatic appearance of DDT when administered in the triglyceride vehicle, compared to the corresponding fatty acid vehicles, is probably indicative of this time dependent process.

During the process of lipid absorption and subsequent chylomicron formation within the enterocytes, the portal blood is essentially acting as an absorption sink competing for absorbable DDT, as the flow ratio of portal blood to intestinal lymph is approximately 500 : 1 (Bollman et al., 1948; Reininger and Saperstein, 1957). That is, the longer DDT remains in the lumen of the small intestine or within the enterocyte, the greater the potential transport of the compound into the portal blood. The importance of the kinetics of lipid absorption affecting the lymphatic transport of a coadministered drug is supported by the different slopes (loadings) of the previously listed DDT transport–CM transport relationships for the different lipid vehicles. The more readily absorbed fatty acid vehicles produced a greater relative concentration of DDT per unit of lymph lipid than when the drug was co-administered in a triglyceride. The total intestinal lymphatic transport of the administered drug was reflected by the concentration of DDT per chylomicron, as approximately equal quantities of lipid were transported in intestinal lymph over the post-dosing period for the 200 μl volume.

It appears that blood and lymph compete for that quantity of DDT which is absorbed from the gastrointestinal tract, as approximately equal quantities of DDT were recovered from the intestinal lumen after administration in either the fatty acid or triglyceride vehicles. The fatty acid based vehicles, which can presumably be processed towards chylomicron formation at a rate faster than the triglyceride vehicle, were able to maintain a higher concentration of the drug in the absorbed lipoidal fraction which was reflected by the higher loading of DDT per lymph lipid than the triglyceride vehicle. The triglyceride vehicle, taking potentially longer before chylomicron formation occurs may lose relatively more DDT from the absorbed lipoidal fraction to the portal blood than did the fatty acid-based vehicles. Again, this is consistent with a lower relative loading of DDT per lymph lipid.

The class of lipid in which a lipophilic drug is formulated can affect the rate and extent of lymphatic transport of a lipophilic drug. Depending upon the pharmacokinetic profile of a particular drug, the input function of the drug via the intestinal lymphatic route could be altered, as desired, by judicious choice of the lipid vehicle in which the drug was formulated. The intestinal lymphatic system, via the cysterna chyli, empties into the venous blood at the junction of the left internal jugular and left sub clavian veins (Youmans, 1962). The data presented here indicate that the appearance of DDT in the intestinal lymph was essentially zero-order over a 6 h time period (see linear portions of the cumulative % dose versus time graphs in Figs. 1 and 3). Therefore, the promotion of the intestinal lymphatic transport of a drug has the potential for controlling the rate of entry of a drug into the systemic circulation.

On a bodyweight conversion basis, the 50 μl dose volume investigated in this study was equivalent to about 10 ml for a 70 kg human. This volume is too large for commercial therapeutic applications. However, if one extrapolates, with

caution, it may be possible to reduce the dose volume to more realistic values for subsequent human administration. This would be dependent on factors such as drug potency, required daily dose of the drug and the quantity of lipid necessary to initiate lymphatic transport in the small intestine of humans.

Diet and dietary lipids may play a significant role in the reproducibility of intestinal lymphatic transport of drug molecules. Much work needs to be done in this area to assess the potential of intestinal lymphatic drug delivery in humans as the majority of research has involved experimental animals. The differing biliary systems of the rat and human, with respect to their control and emptying, may affect lymphatic drug transport after administration of a single dosage form. This also requires careful evaluation.

Acknowledgements

The authors wish to thank Dr. T. Noguchi for helpful discussions. This work was supported by R.P. Scherer Corporation.

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