Influence of the Type of Surfactant and the Degree of Dispersion on the Lymphatic Transport of Halofantrine in Conscious Rats

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Purpose. To compare the lymphatic transport and the portal absorption of halofantrine (Hf) when administered in (i) a triacylglycerol (TG) solution, (ii) an o/w-emulsion that contains a metabolizable surfactant, and (iii) an o/w-emulsion that contains a synthetic surfactant.

Methods. Lymph cannulated rats were orally dosed with Hf in a TG solution or in o/w-emulsions dispersed by lecithin or Cremophor RH40. Lymph was continuously collected, and blood was sampled periodically in the course of 30 h. Hf in the lymph and blood and TG and phosphatidyl choline (PC) in the lymph were analyzed.

Results. A significantly ($p < 0.05$) higher level of Hf was found in the intestinal lymph when dosed in one of the emulsions (22.8 ± 2.8% and 20.2 ± 2.5%) compared to in the TG solution (7.9 ± 1.1%). No difference in the lymphatic transport of Hf was observed between the two emulsions. The portal absorption of Hf was similar for the three vehicles.

Conclusions. The emulsified vehicles favor an increased lymphatic transport of Hf. The portal transport of Hf was not significantly different for the three vehicles. This indicates that a different degree of dispersion of the TG vehicle can change the route of transportation of Hf.

KEY WORDS: Cremophor RH40; dispersion; halofantrine; lecithin; lymphatic transport.

INTRODUCTION

A large proportion of recently discovered drugs are very lipophilic molecules with low and variable bioavailabilities. Many approaches have been made to overcome this problem, including salt formation of acidic or alkaline drugs, incorporation of the drug into cyclodextrine complexes, enhancement of the drug's specific surface area, and administration of the drug in lipid-based formulations. Co-administration of lipids could enhance the absorption of poorly water-soluble drugs via an increased gastrointestinal (GI) residence time, via solubilization of the drug in the GI environment, or through increased lipoprotein formation (1). For lipophilic substances with a log p value above 4.7 and a lipid solubility above 50 mg/ml, this could lead to increased lymphatic transport (2). The lymphatic transport circumvents the liver and reduces the first-pass metabolism, and transport via the lymphatic route is likely to lead to a more uniform and higher bioavailability of the drug. Furthermore, the use of the lymphatic pathway opens up the possibility of targeting lipophilic drugs to various sites in the intestinal and thoracic lymphatic system (2–4). Lipid-based delivery systems that contain long-chain triacylglycerols (LCT) are likely to enhance the lymphatic transport of lipophilic drugs. Lipolysis products of LCT are absorbed by the enterocyte, re-esterified into triacylglycerols (TGs) in the smooth endoplasmic reticulum, and incorporated into chylomicrons or very low density lipoproteins before exocytosis into the lymphatics takes place (5). Lipid-based formulation systems examined with respect to a possible enhanced intestinal lymphatic transport include oil solutions (6), o/w-emulsions (7), micellar solutions (8,9), and self-emulsifying drug delivery systems (10). Porter *et al.* (8) studied the effect that an increasing concentration of the hydrophilic, non-ionic surfactant polysorbate 80 and the effect that dispersion had on the lymphatic transport of halofantrine (Hf) in anesthetized rats. A higher amount of lymphatically transported Hf was found when increased concentrations of the surfactant were present. Similarly, Ichihashi *et al.* (7) showed that compared to a TG solution, a polysorbate 80 dispersed o/w-emulsion induced a higher lymphatic transport of mepitiostane in bile diverted anesthetized rats, which indicates that an increased dispersion increases the lymphatic transport and the total absorption. In contradiction to these findings, Porter *et al.* (9) saw no change in the lymphatic transport of Hf in conscious rats upon administration of a polysorbate 80 micellar predigested TG solution and a TG solution.

Lecithin, which is a complex mixture of phosphatides, such as phosphatidyl choline (PC), phosphatidyl ethanolamine, phosphatidyl serine, and phosphatidyl inositol, is hydrolyzed in the GI tract, absorbed and cycled in the endogene phospholipid metabolism. Infusion of PC with TG in both bile-intact as well as bile-diverted rats has shown to increase the lymphatic transport of TG (11,12). It is likely that the observed effect is a PC-promoted alteration of the enterocytic TG transport pathway and rate (12). Cremophor, which is a polyoxyethylene hydrogenated castor oil, is a commonly used surfactant in the pharmaceutical industry. Cremophor as well as castor oil are expected to have a limited absorption *in vivo* (13).

Studies of the effect that surfactants have on the lymphatic transport of a lipophilic drug are still limited in number. The current study has been designed to investigate (i) the effect that a metabolizable and a synthetic surfactant have on the lymphatic transport, and (ii) the dispersion effects that an emulsion has on the amount of TG transported in the lymph and the amount of drug transported in lymph and blood compared to a TG solution.

MATERIALS AND METHODS

Materials

The Hf crystalline base and the internal standard 2,4-dichloro-6-triflurometh yl-9[1-[2-(dibutylamino)ethyl]]phen-

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ABBREVIATIONS: AUC, area under the plasma curve; DDT, 2,2-bis (*p*-chlorophenyl)1,1,1-trichloroethane; p,p-DDT); FA, fatty acid; GI, gastrointestinal tract; Hf, halofantrine; LCT, long-chain triacylglycerol; o/w, oil/water; PC, phoshatidyl choline; P-gp, P-glycoprotein; rp-HPLC, reversed-phase high-performance liquid chromatography; TG, triacylglycerol.

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athrenemethanol hydrochloride were donated by GlaxoSmithKline (West Sussex, UK). Lipoid GmbH (Ludwigshafen, Germany) kindly provided Lecithin S-75 (70% PC). Soybean oil was purchased from Unikem (Copenhagen, Denmark), Cremophor RH40 was from BASF (Ludwigshafen, Germany), and glycerin (>98%) and propylene glycol (>99.5%) were from Riedel-de Haën AG (St. Gallen, Germany). Purified water was obtained from Millipore Milli-Q Ultrapure Water Purification Systems (Billerica, MA, USA). Acetonitrile and *tert*-butylmethylether constituted the high-performance liquid chromatography (HPLC) grade, and sodium dodecyl sulfate was of electrophoresis grade. All other chemicals were of analytical reagent grade.

TG Delivery Systems Containing Hf

Formulation of the Oral TG Solution and the Oral O/W-Emulsions

In order to prepare the TG solution, 0.5 w/w% Hf was dissolved in soybean oil during magnetic stirring. For the o/w-emulsion, 0.1 w/w% Hf was dissolved in soybean oil (20 w/w%). The surfactant (2 w/w%), which was either lecithin or Cremophor, was dissolved in the soybean oil solution by gently heating it in a water bath (50°C) during continuous magnetic stirring. Propylene glycol (15 w/w%) and glycerol (15 w/w%) were added to the oil phase during 3 min of homogenization at 13,500/min (Ultraturrax T25, IKA-labortechnik, Janke & Kunkel, Staufen, Germany). Subsequently, purified water (47.9 w/w%) was added, and the mixture was emulsified by means of a homogenizer equipped with a standard microtip at power output 5 (Sonifier Cell Disruptor, Model B15, Branson, Pusan, Korea).

Formulation of the Intravenous O/W-Emulsion

The intravenous emulsion contained 0.1 w/w% Hf, 20 w/w% soybean oil, 2 w/w% lecithin, 2.5 w/w% glycerol, and 75.4 w/w% water. Prepared in the same manner as the oral lecithin emulsion, it was cycled for an additional 4 min in a high-pressure homogenizer (EmulsiFlex-C5, Avestin Inc, Mannheim, Germany) and aseptically filtered through a sterile 0.45-μm filter and a 0.22-μm filter (Millipore, Billerica, MA, USA) into a sterilized glass bottle.

Characterization of TG Delivery Systems

The droplet sizes of the emulsions were monitored by means of laser diffraction (lens 300RF; Malvern Mastersizer S, Malvern Instruments Ltd., Worcestershire, UK), and the contents of Hf were monitored by means of HPLC. The tonicity of the intravenous emulsion was controlled by means of freeze point depression measurements (Osmomat 030-D, Gonotec, Berlin, Germany). Furthermore, the TG formulations were visually inspected for physical changes.

Animal Surgery

All surgical and experimental procedures were reviewed and approved by the Danish Animal Experimentation Ethics Committee and adhered to the *Guide for the Care and Use of Laboratory Animals* (NIH publication, 1996). Male Spraque-Dawley rats (280–380 g) were purchased from Moellegaard Breeding & Research Center A/S (Skensved, Danmark) and maintained on a standard diet containing 2.71% fat (RM1, Special Diets Services, Essex, UK). They were allowed free access to food and water until the time of surgery. Thirty minutes prior to surgery, the rats were dosed 0.3 ml/kg soybean oil to aid identification of the lymph duct. Anesthesia was induced and maintained with a mixture of Hypnorm (0.2 mg/ml fentanyl, 10 mg/ml fluanisone; Janssen, Belgium), Dormicum (5 mg/ml midazolam; Roche, Switzerland), and sterile water (1:1:2).

Following a ventral midline incision, the major mesenteric lymph duct was cannulated using a polyvinylchloride tube (0.8 mm o.d. × 0.5 mm i.d.; Critchley Electrical Products Pty Ltd, Silverwater B.C., NSW Australia) using a slightly modified method, which has been described previously (14). The catheter was secured with ethyl-2-cyanoakrylate (Casco expresspipetter, Nacka, Sweden), passed over the vena cava, and exteriorized through stab wounds in the right flank. The minor mesenteric lymph duct was destroyed to divert the lymph flow to the cannulated lymphatic duct. In rats receiving one of the oral formulations, the left carotid artery was cannulated using a tygon S-50-HL tube (0.8 mm o.d. × 0.4 mm i.d.; Dilab, Lund, Sweden). Additionally, the left external jugular vein was cannulated in rats assigned to the intravenous formulation. The intravenous group was not cannulated in the mesenteric lymph duct, as previous results showed that a negligible amount of Hf was transferred from the blood to the lymph (15). Post surgery rats were given subcutaneously 0.1 ml/kg of Rimadyl Vet (50 mg/ml carprofen; Pfizer, New York, NY, USA).

Experimental Procedures

During the 20- to 24-h recovery period, the rats had free access to lump sugar (Danisco, Copenhagen, Denmark) and water containing 5% dextrose (Nutana, Bjæverskov, Denmark). During recovery and the experimental phase, the arteries were infused with 210 μl/h of 25 IE/ml heparin (LEO Pharma, Ballerup, Denmark) administered in sterile isotonic saline in order to prevent blocking of the catheters. Twelve rats, which had been randomly assigned to receive one of the three oral formulations, were dosed 6.7 mg Hf/kg and 1.3 g TG/kg by way of oral gavage. For the TG solution, an additional 5.3 g distilled water/kg was given in order to ensure a 6.7 g dose weight/kg in all of the oral treatments. In the course of 30 h, the lymph was collected in tared vials, which were changed every hour in the period 0–12 h, at 24 h, and at 30 h after drug administration. The lymph collected at 1-h intervals was collected in 2-ml borosilicat glass vials with a screw cap (National Scientic Company, Duluth, GA, USA) containing 20 μl 200 IE/ml heparin saline. The lymph collected with long interval was sampled into 6 ml polyethylene vials (Packard BioScience, Zaventem, Belgium) containing 100 μl 200 IE/ml heparin saline. Lymph samples were stored at −30°C until analysis. Blood samples (250 μl) were collected in 1.5-ml Eppendorf tubes containing 20 μl 200 IE/ml heparin saline at 0, 1, 2, 4, 6, 8, 10, 12, 24, and 30 h after drug administration. Plasma was immediately harvested by 10 min of centrifugation at 4°C, 15,000 × *g* (rotor 5.4 cm, Microcentrifuge 157, Ole Dich Instrumentmakers, Hvidovre, Denmark) and stored at −30°C until analysis.

Four rats were dosed 1.7 mg of Hf/kg via the intravenous lecithin emulsion in the left jugular vein in the course of

1 min. Blood samples of 100 μl were withdrawn at –1, 10, 20 min, 1 h, and 2 h, whereas samples of 250 μl were withdrawn at 4, 6, 8, 10, 12, 24, and 30 h after drug administration. Following the 30-h experimental period, the animals were sacrificed by an overdose of sodium pentobarbital.

Quantitative Analysis of Hf, TG, and PC

Analysis of Hf in Lymph and Plasma Samples

Hf was monitored quantitatively in the TG formulations and in the blood and lymph samples by means of rp-HPLC. This included a Merck Hitachi system, series 7000 (Hitachi, San Jose, CA, USA), and the separation was accomplished by means of a Luna 5 μm C8(2), 4.6 × 250 mm analytical column with a Phenomenex Security Guard column, C8 4 × 3.0 mm. The lymph samples were analyzed by means of a slightly modified HPLC method, which previously has been described (8). One hundred microliters of lymph sample was added 8 ml mobile phase and was vortexed for 1 min. The proteins were isolated by means of centrifugation for 10 min at 1000 × *g* (Labofuge 400R, Hanau, Germany), and 25 μl supernatant was analyzed on the HPLC. A standard curve of Hf in blank lymph was linear in the range 5–130 μg/ml ($r^2 > 0.99$), and recovery for Hf was more than 99% in the concentration range.

Plasma samples were analyzed by following a slightly modified HPLC method (16). One hundred microliters of plasma sample was spiked 20 μl internal standard (10 μg/ml in acetonitrile), 1 ml acetonitrile, and 4 ml *tert*-butylmethylether and was vortexed consecutively for two times 30 s. The contents were centrifuged at 700 × *g* for 5 min (Labofuge 400R, Hanau, Germany). Four milliliters of the upper layer was added to 100 μl 5 mM HCl in acetonitrile and was evaporated to dryness under a stream of high-purity N_2 at 35°C. The residue was reconstituted with 100 μl mobile phase, and 25 μl was analyzed by HPLC. A standard curve of Hf in spiked blank plasma was linear in the range 20–2600 ng/ml ($r^2 > 0.99$), and recovery for Hf was more than 90% in the concentration range.

Analysis of TG and PC in Lymph Samples

PC and TG were analyzed by means of enzymatic colorimetry, using commercially available kits (Roche Diagnostics, Basel, Switzerland). Samples were run on a validated Cobas Mira analyzer (Roche).

Pharmacokinetic and Statistical Analysis

The concentration of Hf in plasma was analyzed using WinNonLin Professional, version 3.3, build 24. The plasma concentrations of Hf upon oral administration were fitted into a noncompartmental model, whereas the Hf plasma concentrations upon intravenous administration were modeled into a two-compartment model. After intravenous administration, the areas under the plasma curve (AUC) were extrapolated from the last measured concentration (30 h) to infinity using the linear trapezoidal rule. The bioavailability of portal absorbed Hf was calculated as $F = (AUC_{e.v.}/AUC_{i.v.}) \times (Dose_{i.v.}/Dose_{e.v.})$. The cumulated percentage of the dosed Hf found in the lymph was calculated as the concentration in the lymph fraction multiplied by the total weight of the lymph collected.

Using Microsoft Excel 97, statistical analyses were performed by means of a single factor analysis of variance for the blood bioavailability and the cumulated percentage of the dosed Hf found in the lymph. The Student's *t* test was used in order to analyze differences between the formulations. The results were considered significant when $p < 0.05$.

RESULTS AND DISCUSSION

Recent interest in preparing pharmaceutically acceptable lipid-based drug delivery systems for hydrophobic drugs has led to an increased use of metabolizable and less toxic surfactants, such as phospholipids (17,18). Whereas previous studies have examined primarily the technical properties of these surface active compounds, the current study focuses on the absorption properties of the highly lipophilic Hf when administered in a vehicle containing lecithin or the frequently used non-ionic surfactant Cremophor RH40.

Formulation of TG Delivery Systems Containing Hf

Visual inspection of the drug-free emulsions, which contained 2% lecithin or Cremophor as a surfactant, showed that whereas glycerol is a suitable co-solvent for the lecithin dispersed emulsion, propylene glycol is a better co-solvent for the Cremophor system. Thus, a mixture of glycerol and propylene glycol (1:1) was used in the two emulsions. Lecithin and Hf in concentrations higher than 2% and 0.1%, respectively, caused physical changes in solution, which were probably due to an insertion of Hf into the hydrocarbon interior of the phospholipid bilayer (19). When the surfactant concentration in the o/w-emulsions constituted 2%, high concentrations of the co-solvents, glycerol and propylene glycol, were needed to obtain stable emulsions with similar droplet sizes. The droplet sizes of the oral lecithin and the Cremophor emulsion were not significantly different from one another, having average droplet sizes of 445 ± 16 nm (n = 4) and 455 ± 14 nm (n = 4), respectively. Emulsions were monomodal and had span values of 1.18 and 1.58. The quantitative amounts (mean ± SE) of Hf measured in the TG formulations were 1.00 ± 0.03 mg/g, 0.96 ± 0.02 mg/g, and 4.33 ± 0.11 mg/g (n = 4) for the lecithin emulsion, the Cremophor emulsion, and the TG solution, respectively. The intravenous lecithin emulsion, which contained 2.12 mg/g Hf, had an average droplet size of 380 nm with a span value of 1.02 (n = 1). No physical changes was observed or measured within 1 week of preparation.

Transport of TG and PC in Rat Intestinal Lymph

The cumulated percentage of the dosed TG transported in the mesenteric lymph after administration of the TG solution and the two emulsions as a function of time is presented in Fig. 1. In the course of 30 h, 35.2 ± 3.3%, 27.5 ± 2.4%, and 29.6 ± 6.4% (mean ± SE) were recovered upon administration of TG in the lecithin emulsion, the Cremophor emulsion, and the TG solution, respectively. A previous experiment showed 67–121% lymphatic TG recovery after administrations of 270 mg of different TGs (20). In the current study, the low TG transport in the lymph could be explained by an overload of the TG transport through the enterocyte. The transit time in the small intestine of the rat is estimated to 88 min (21), but the transport of TG into the lymph had not ended 2 h upon

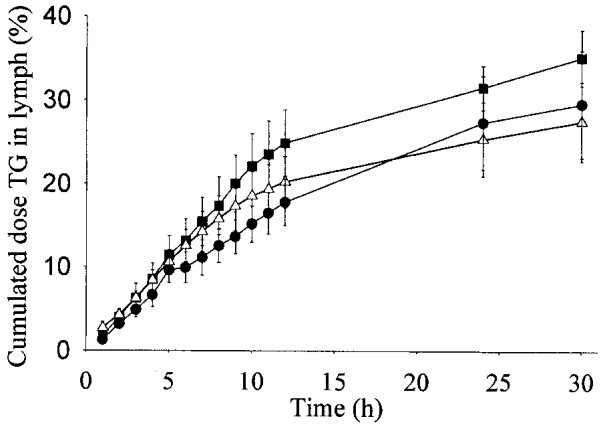

Fig. 1. Cumulated percentage of the dosed TG (mean ± SE, n = 4) transported in the mesenteric lymph as a function of time upon administration of 6.7 mg Hf/kg and 1.3 g TG/kg in either a lecithin emulsion (■), a Cremophor emulsion (△), or a TG solution (●). Numbers refer to endogenous and exogenous TG transported.

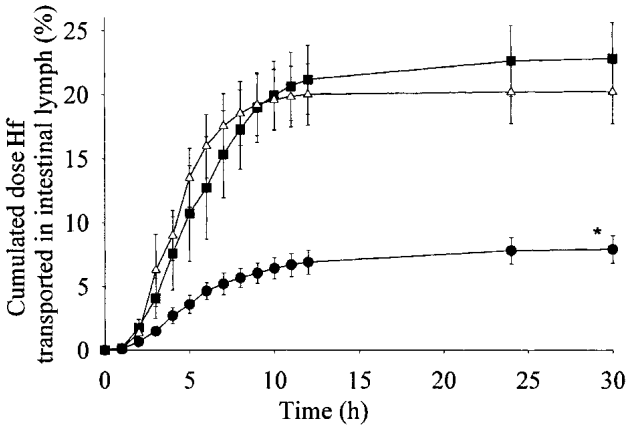

Fig. 2. Cumulated percentage of the dosed Hf (mean ± SE, n = 4) which is transported in the mesenteric lymph as a function of time after oral administration of 6.7 mg Hf/kg and 1.3 g TG/kg in either a lecithin emulsion (■), a Cremophor emulsion (△), or a TG solution (●). The asterisk indicates where the cumulated % dose of Hf is statistically different between the emulsions and the TG solution.

administration as seen in Fig. 1. The TG, which is observed in the lymph a few hours upon administration, is thus suggested to originate from the FA absorbed into the enterocyte, where it is subject to accumulation and slowly excretion. This is consistent with results obtained by Tso *et al.* (22), who found that almost all of the lipid (92.5%) was absorbed upon intraduodenal infusion of triolein and that absorption took place in the first part of the small intestine. However, the secretion into the lymph was less than 50%, which indicates a saturation of the secretion process and an accumulation of lipid inside the enterocyte. Similarly, Hussain *et al.* proposed that, rather than synthesis of TG, secretion is the rate-limiting step in the enterocyte (23).

After 30 h, the cumulated amounts of PC in the mesenteric lymph were 69.1 ± 18.8 mg, 32.9 ± 1.3 mg, and 36.3 ± 5.1 mg upon administration of the lecithin emulsion, the Cremophor emulsion, and the TG solution. After administration of the TG solution and the Cremophor emulsion, the observed lymphatic transport of PC is caused by endogenous presence of PC. Subtracting this endogenous circulation of PC from the transport of PC upon administration of the lecithin emulsion, the average absorption of PC from the lecithin emulsion approximated 90% of the administered dose. Whereas 90% of the dosed PC was recovered in the lymph, only 28–35% of the TG was transported in the lymph. They are both expected to be dispersed in the same micellar phase during passage through the unstirred water layer, which is consistent with the above statement concerning the saturation of the TG secretion. In contrast to previous findings (11,12), dosing approximately 100 mg/kg PC in the lecithin emulsion did not increase the lymphatic transport of TG significantly.

Transport of Hf in Rat Intestinal Lymphatics

The lymphatic transport of Hf is illustrated in Fig. 2 as the cumulated percentage of the administered dose as a function of time. The amount of lymphatically transported Hf was 7.9 ± 1.1% (mean ± SE) of the administered dose after its administration in a TG solution, which was similar to a previously published result (6). Upon administration of the lecithin and the Cremophor emulsions, 22.8 ± 2.8% and 20.2 ± 2.5% (mean ± SE) of the dosed Hf was transported in the mesenteric lymph duct, which was comparable to previous results obtained from dispersed systems (9). The lymphatic transport of Hf was significantly higher upon administration of the emulsions compared to the TG solution. The absorption of Hf into the mesenteric lymphatics approximated zero-order kinetics, and in the experimental interval of 2–7 h, linear absorption was observed for all of the three TG formulations ($R > 0.90$). By linear regression, the average absorption rates had the estimated values of 2.8, 3.7, and 1.2%/h for the lecithin emulsion, the Cremophor emulsion, and the TG solution, respectively. This indicates a faster rate of absorption of Hf into the lymphatics upon administration of the emulsions when compared to administration of the TG solution.

One possible explanation for the enhanced lymphatic transport of Hf upon administration of the emulsions is that the increased dispersion of the oil droplets initiates a faster hydrolysis by the gastrointestinal lipases due to the larger surface area. The increased rate of lipolysis results in a faster incorporation of Hf in the micelles and a faster penetration of the unstirred water layer. This is likely to lead to a more proximal absorption and an increased absorption rate compared to the TG solution. Contrary to this, the TG solution needs longer time for GI emulsification and lipolysis, which is likely to increase the risk of precipitation in the GI. This is consistent with previous findings where the effect of the dispersion degree has been investigated on the *in situ* intestinal absorption of cyclosporin A. It was found that the smaller the emulsion droplets were, the faster the pancreatic lipase broke down the oil droplets and the higher was the total intestinal absorption (24). Ichihashi *et al.* examined the regional transport of mepitiostane from different segments of the intestine to the mesenteric lymph and found that the upper part of the intestine gave the highest amount of lymphatically transported drug. When absorption took place farther down in the intestine, an increased amount of drug was absorbed portally (7). Porter *et al.* examined the effect that different dispersion degrees had on the lymphatic transport of intraduodenal ad-

ministered Hf in anesthetized rats. It was found that an increased dispersion enhanced the lymphatic transport (8). Contrary to these findings, the same research group found no differences in the lymphatic transport of Hf upon its administration in a dispersed phase and in a TG solution in conscious rats (9). It was concluded that the dispersion effect on the lymphatic transport of Hf was seen only in anesthetized rats due to decreased gastric motility and solubilization of this animal model. However, in these studies only 50 μl lipid was administered as opposed to 400 μl in the current study. The administered amount of lipid is important, as the endogenous capacity of surfactants is assumed to emulsify lipids in a dose-dependent manner.

Alternatively, the increased lymphatic transport of Hf caused by the emulsions could be related to effects caused by the surfactants. The increased lymphatic transport of Hf, which was observed upon administration of a lecithin emulsion, could be a result of a PC-promoted increase in lipoprotein secretion (25). Furthermore, it is possible that the increased lymphatic transport of Hf, which occurred after administration of the Cremophor emulsion, could be a result of a Cremophor-mediated alteration in the lipoprotein secretion or in the P-gp efflux mechanism. In a study of human leukemic cell lines, Woodcock *et al.* (26) demonstrated that Cremophor is able to inhibit the P-glycoprotein efflux of daunorubicin. Although not fully clarified, there is a possibility that Hf interacts with the intestinal P-gp (27), leading to a competition for the intestinal active efflux mechanism between the Cremophor and the Hf.

The cumulated percentage of the dosed Hf transported in the mesenteric lymph during 30 h as a function of the cumulated percentage of the dosed TG is presented in Fig. 3. The lymphatically transported Hf is linearly related to the TG transported in the mesenteric lymph in the period 0–9 h for all of the three formulations ($R^2 > 0.95$). However, the ratio of lymphatically transported Hf/TG is much higher for the emulsions than for the TG solution. Transport of Hf is minimal after 10 h, and it did not seem to be retained in the enterocyte to the same extend as the TG. Two previous studies found no indication that the volume of dosed lipid had any influence on

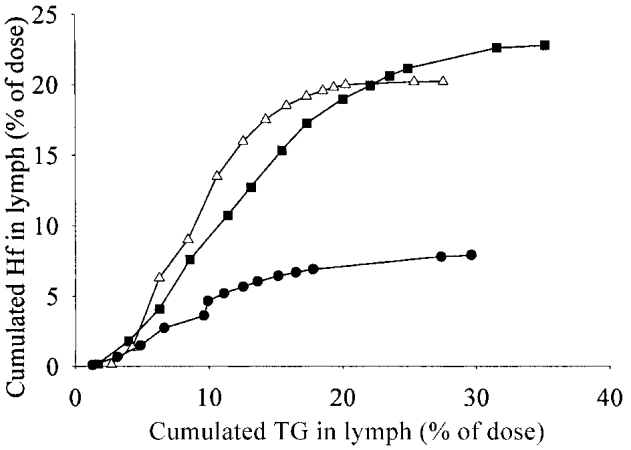

Fig. 3. Cumulated percentage of the dosed Hf as a function of cumulated percentage of the dosed TG (mean, n = 4) transported in the mesenteric lymph upon administration of 6.7 mg Hf/kg and 1.3 g TG/kg in either a lecithin emulsion (■), a Cremophor emulsion (△), or a TG solution (●).

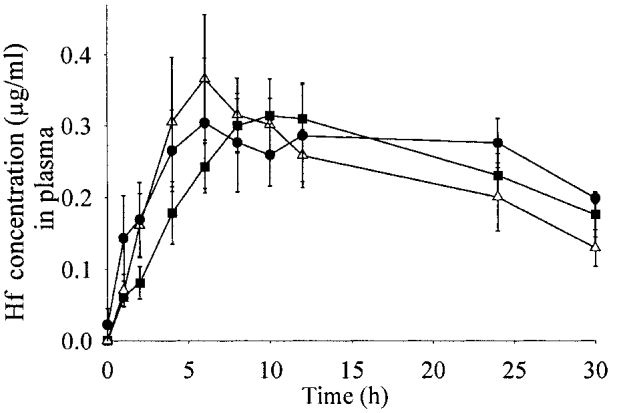

Fig. 4. Plasma concentrations (mean ± SE, n = 4) of Hf as a function of time upon administration of 6.7 mg Hf/kg and 1.3 g TG/kg in either a lecithin emulsion (■), a Cremophor emulsion (△), or a TG solution (●).

the amount of lymphatically transported DDT or benzo(a)pyrene upon intraduodenal administration of FA, FA and monoglyceride, or TG in the range 50–470 mg in anesthetized rats (28,29). If a small amount of lipid induces the same lymphatic transport of a lipophilic compound as a large lipid load and if a large lipid load can be accumulated inside the enterocyte due to a saturated secretion, then it is possible that there is more than one pathway for the enterocytic transport of lipids and lipophilic compounds.

Portal Transport of Hf

The concentration of portally absorbed Hf as a function of time after oral administration in the three TG formulations is illustrated in Fig. 4. The portal absorption of Hf was found to approximate a first-order process by the method of residuals. No difference was found in the plasma bioavailabilities of Hf after oral administration of the three TG formulations (Table I). The plasma bioavailabilities in this study are slightly higher than previously observed (6). Charman *et al.* suggested that the longer DDT remained within the enterocyte, the greater was the potential transport of the compound into the portal blood. This could be due to an enhanced sink condition caused by the high flow rate in the portal blood (28). Similarly, the slightly elevated portal transport of Hf in this study could be explained by a partition of Hf into the accumulated TG within the enterocyte.

CONCLUSIONS

Compared to a TG solution, the o/w-emulsions in the current study have revealed a significantly higher lymphatic transport of Hf when administered to conscious rats. This is likely to be caused by a faster lipolysis of the dispersed formulations leading to an absorption in the early part of the GI. Alternatively, the increased lymphatic transport of Hf could be due to surfactant-specific properties. However, no statistical differences were found in the lymphatic transport upon administration of the emulsions, which contained synthetic or metabolizable surfactants. Using the same amount of surfactant in emulsions with different droplet sizes in a study of the lymphatic transport could clarify whether the effect seen is due to dispersion or related to the surfactant. Whether the increased lymphatic transport of Hf, as seen with the o/w-

Table I. Mean Bioavailabilities (± SE) of Hf upon Administration in Three TG Formulations

	Portal blood F (%)[a]	Mesenteric lymph[b] cumulated dose (%)
Lecithin emulsion	20.9 ± 1.8	22.8 ± 2.8
Cremophor emulsion	20.8 ± 3.6	20.2 ± 2.5
TG solution	24.4 ± 3.9	7.9 ± 1.1[c]

Hf, halofantrine; TG, triacylglycerol.

[a] The amount of lymph collected in the course of the experimental 30 h was 15.0 ± 1.1 g, 15.2 ± 2.5 g, and 14.0 ± 1.5 g (mean ± SE) after administration of the lecithin emulsion, the Cremophor emulsion, and the TG solution.

[b] The bioavailability of the Hf that was absorbed into the portal blood was calculated as $F = (AUC_{e.v.}/AUC_{i.v.}) \times (Dose_{i.v.}/Dose_{e.v.})$. The AUCs after administration of the lecithin emulsion, the Cremophor emulsion, the TG solution, and the intravenous emulsion were 7.0 ± 0.7, 6.9 ± 1.3, 7.7 ± 1.0, and 8.0 ± 0.9 h · μg/ml, respectively.

[c] Statistical difference from the cumulated amounts upon administration of the emulsions ($p < 0.05$).

emulsions, is reflected in an increase in the bioavailability in lymph-intact conscious rats is yet to be clarified.

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