Intestinal Lymphatic Transport of Halofantrine Occurs after Oral Administration of a Unit-Dose Lipid-Based Formulation to Fasted Dogs

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Purpose. To examine whether the small quantities of lipid present in unit-dose microemulsion formulations comprising medium- (C_{8-10}) or long-chain (C_{18}) glyceride lipids can stimulate the intestinal lymphatic transport of halofantrine (Hf), a model lymphatically transported drug.

Methods. Hf (50 mg) was administered to thoracic lymph duct– and cephalic vein–cannulated fasted greyhound dogs. Drug was formulated as a single soft gelatin capsule containing approximately 1 g of a microemulsion preconcentrate based on either medium- or long-chain glycerides. Thoracic lymph was collected, and systemic plasma samples taken over 10 h postdose.

Results. The extent of lymphatic transport of Hf after administration of the long-chain lipid formulation was high (28.3% of dose), and significantly higher than that seen after administration of the medium-chain formulation (5.0% of dose). Plasma levels of Hf were not significantly different across the two formulations when assessed by AUC_{0-10h}.

Conclusions. This is the first study to demonstrate that the small amounts of lipid present within a single lipid-based dose form can support substantial intestinal lymphatic transport in the fasted state. Furthermore, microemulsions based on long-chain glycerides appear to be more effective with respect to lymphatic transport than the equivalent medium-chain formulation.

KEY WORDS: intestinal lymphatic transport; lipid formulation; fasted; halofantrine; QTc.

INTRODUCTION

The intestinal lymphatics are a specialized absorption pathway through which highly lipophilic xenobiotics and drugs can gain access to the systemic circulation (1,2). Lymphatic transport of lipophilic drugs is facilitated by their association with enterocyte-derived lipoproteins, which are assembled in response to lipid absorption and digestion. For intestinal lymphatic transport to be a significant contributor to oral bioavailability, candidate drugs are typically highly lipophilic [log $P > 5$, with significant solubility in long-chain triglycerides (3)] and administered either postprandially or with an appropriate lipid source (2).

The intestinal lymphatic transport literature consists almost entirely of studies conducted in rats, where attainment of pre- and postprandial intestinal environments representative of humans is not possible (bile flow in the rat is continuous and is not stimulated by ingested food). Furthermore, it is not possible to use rats to evaluate clinically relevant dose forms because of inherent size, formulation, and compositional issues (4,5).

To address limitations of the rat lymph model, we developed and validated a conscious dog model that enables continuous collection of thoracic duct lymph (6). Dogs can ingest dose forms identical to those used in human medicine, and their fasting and postprandial intestinal environments are representative of the relevant human states (7). The intestinal lymphatic transport of halofantrine (Hf), a highly lipophilic antimalarial, after fasted or postprandial oral administration to dogs as a lipid-free formulation was 1.3% and 54% of the administered dose, respectively (6). When compared with rat data (8), the postprandial intestinal lymphatic transport of Hf in the dog was more extensive and rapid.

The aim of the current study was to investigate the intestinal lymphatic transport of Hf in fasted dogs administered a unit-dose medium-chain or long-chain microemulsion. This is the first study to identify the significant effect that small amounts of lipid present within a single lipid-based dose form can have on the transport of a lymphatically transported drug administered in the fasted state. The reported data have implications with regard to (a) the recruitment of the lymphatics as an absorption pathway after fasted administration of a lipid-based formulation, (b) altered drug delivery profiles as lymphatically transported drugs access the mesenteric lymphatics and associated lymph nodes and then empty into the systemic circulation at the junction of the left subclavian vein and the jugular vein, (c) possible changes in the pharmacokinetics and systemic clearance of lipophilic drugs, (d) the potential stimulation of lymphatic transport when a lipophilic drug is ingested in a partial-prandial state (e.g., as a consequence of the presence of a small amount of dietary lipid from a snack or previously consumed meal), and (e) safety assessment of lipophilic new drug candidates, which are often administered in conjunction with lipids and/or lipidic excipients to enhance drug exposure.

MATERIALS AND METHODS

Materials

Hf base (GlaxoSmithKline, India), Cremophor EL (BASF, Germany), Maisine 35-1 (Gattefossé s.a., Saint-Priest, France), super-refined soybean oil (Croda Surfactants, Australia), Capmul MCM, and Captex 355 (Abitec Corporation, Janesville, WI) were used as received. One-milliliter air-filled oblong soft gelatin capsules were kindly provided by R. P. Scherer (Australia). All other chemicals were analytical reagent grade, and solvents were HPLC grade. Water was obtained from a Milli-Q (Millipore, Milford, MA) water purification system.

Methods

Preparation of Lipid-Based Formulations

The medium- and long-chain microemulsion formulations were similar to those previously described (9). Each 1-g

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unit-dose of the medium-chain microemulsion preconcentrate formulation (ME-MC) contained Hf base (50 mg), Captex 355 (290 mg), Capmul MCM (290 mg), Cremophor EL (300 mg), and absolute ethanol (70 mg). The corresponding long-chain microemulsion preconcentrate (ME-LC) comprised Hf base (50 mg), soybean oil (290 mg), Maisine 35-1 (290 mg), Cremophor EL (300 mg), and absolute ethanol (70 mg). Formulations were prepared and individually filled into soft gelatin capsules as described previously (9).

The dispersion and emulsification characteristics of the formulations were assessed as previously described (9). Briefly, a capsule containing 1 g of either formulation was added to 200 ml of 0.1 N HCl maintained at 37°C in a USP II dissolution apparatus. Gentle agitation was provided by a stainless steel dissolution paddle mounted immediately below the solution meniscus and operated at 60 rpm. Capsules typically ruptured within 10 min to produce a characteristically clear/slightly bluish microemulsion. The mean particle sizes, determined by photon correlation spectroscopy (9), were 39.4 nm and 39.9 nm for the long-chain and medium-chain microemulsions, respectively.

Surgical Procedures

All surgical and experimental procedures were approved and conducted in accordance with the guidelines of the local Institutional Animal Experimentation Ethics Committee. Following induction of surgical anesthesia, the thoracic duct of healthy adult male greyhound dogs (28-35 kg) was cannulated as previously described (6). The dogs were allowed to recover unrestrained for a period of 14 to 16 h after surgery, during which time they remained fasted but with free access to drinking water. A catheter was inserted into the cephalic vein before drug administration to enable serial sampling of peripheral blood during the study period.

Experimental Procedures

In a parallel study design, thoracic lymph duct–cannulated dogs (fasted for 12 h after surgery on the previous day) were orally administered a single (1 g) soft gelatin capsule containing Hf base (50 mg) formulated as either a medium-chain or long-chain lipid formulation, followed by 50 ml of water. Dogs had free access to drinking water during the study period, and any potential dehydration from continuous collection of thoracic lymph was limited by regular, hourly intravenous injections of 25 ml of 0.9% normal saline solution. Food was withheld until after collection of the 10-h lymph and blood samples. Lymph was continuously collected into 50-ml tubes containing 75 mg disodium EDTA during the 10-h postdosing period. The total mass of lymph collected per hour was determined gravimetrically, and lymph samples were stored at 5 to 8°C before analysis within a 24-h period. Systemic blood samples (2.5 ml) were obtained via the indwelling cephalic vein catheter at predose (–5 min) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 10 h postdose. Blood samples were anticoagulated with dipotassium EDTA, and plasma separated by centrifugation and stored at –20°C until analysis.

Analytical Procedures and Pharmacokinetic Analysis

Hf concentrations were determined in plasma and lymph using validated extraction and analytical HPLC methods (6,10), and the concentration of TG in lymph and plasma was measured as described previously (6). The area under the plasma concentration–time curves ($AUC_{0\text{-}t}$) was calculated using the linear trapezoidal rule from time zero to the last measured plasma concentration. The peak plasma concentration (C_{max}) and the time for this occurrence (T_{max}) were noted directly from the individual profiles. The absolute mass of Hf recovered in thoracic lymph was determined by multiplying the concentration of Hf in lymph by the corresponding mass of lymph collected during each time period, and these data were then expressed as a cumulative fraction of the administered dose recovered in thoracic lymph for each dog over 10 h. Statistical differences between the medium-chain and long-chain formulations were assessed using a two-sample *t*-test (Excel 2002, Microsoft Corporation, WA).

RESULTS AND DISCUSSION

It is commonly assumed that the coadministration or ingestion of significant quantities of lipid is a prerequisite for substantial intestinal lymphatic drug transport; however, the actual lipid and volume dependences of the initiation and support of lymphatic drug transport is unknown. In this report, we describe the impact of pharmaceutically relevant volumes of formulated medium- and long-chain lipids on the intestinal lymphatic transport of Hf after fasted oral administration to conscious thoracic lymph duct–cannulated dogs.

Intestinal Lymphatic Transport of Halofantrine

The current study has demonstrated that the oral administration of small, pharmaceutically relevant volumes of formulated long-chain lipid (~600 mg) to fasted dogs can, surprisingly, stimulate and then support lymphatic transport of Hf. The cumulative lymphatic transport of Hf after fasted oral administration in either a medium-chain or long-chain microemulsion to conscious thoracic lymph duct–cannulated dogs is presented in Fig. 1, and Table I is a compilation of the current data and previous relevant transport and pharmacokinetic data. After fasted administration of the long-chain microemulsion, the cumulative lymphatic transport of Hf was a surprisingly high 28.3 ± 7.6% of the administered dose (mean ± SD, n = 4), whereas the extent of transport after administration of the medium-chain microemulsion was five- to six-fold lower at 5.0 ± 0.95% of the dose (mean ± SD, n = 3). By way of historical comparison, lymphatic transport of Hf after fasted or postprandial administration of a lipid-free PEG melt formulation was 1.3% and 54% of the administered 100-mg dose, respectively (6) (Table I). Importantly, the low extent of lymphatic transport of Hf seen after fasted administration of the lipid-free PEG melt was not simply a function of poor overall absorption because the absolute oral bioavailability of Hf after oral administration of this formulation to beagle dogs has previously been shown to be 44% (19).

The coincident cumulative lymph TG transport over the same 0 to 10-h postdosing period was 3.4 ± 2.2 g (mean ± SD, n = 4) and 0.9 ± 0.2 g (mean ± SD, n = 3) after administration of the long- and medium-chain formulations, respectively. The comparative cumulative lymph TG transport (0–10 h postdosing) after similarly lymph-cannulated dogs had previously been administered a lipid-free formulation in

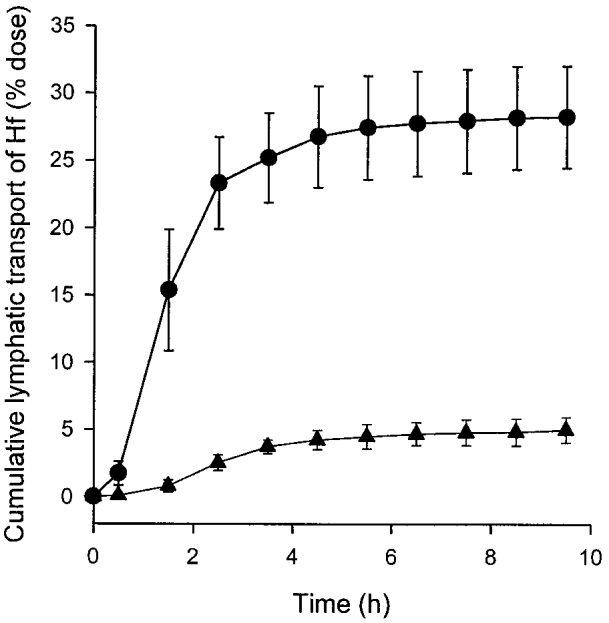

Fig. 1. Cumulative intestinal lymphatic transport of halofantrine (Hf) in thoracic lymph duct–cannulated dogs after fasted oral administration of 50 mg Hf base formulated in either a long-chain microemulsion formulation (●, mean ± SD, n = 4) or a medium-chain microemulsion formulation (▲, mean ± SD, n = 3).

the fasted state was 0.5 g, which increased to 32.6 g after postprandial administration (Table I) (6).

If the absorption and lymphatic transport of the exogenous formulation lipid was quantitative, then the expected mass of recoverable TG in lymph over 10 h (from exogenous and endogenous sources) would have been approximately 1 g, comprising 600 mg exogenous formulation lipid plus 500 mg baseline endogenous TG transport (TG transport after fasted administration of lipid-free PEG melt formulation, Table I). However, the cumulative TG transport after administration of the long-chain microemulsion was 3.4 g, which represents an approximate five-fold increase in the apparent extent of endogenous TG transport (assuming complete absorption and transport of the exogenous formulation long-chain lipid). In contrast, cumulative TG transport after administration of the medium-chain formulation was 0.9 g and broadly within the previously observed range of baseline lymph TG transport (Table I). This is consistent with the medium-chain lipid having little impact on endogenous lipid turnover, most likely because its digestion products are absorbed primarily via the portal blood. It has been reported that lymphatic TG transport in rats after intraduodenal infusion of long-chain fatty acid may exceed the mass of infused lipid and that the TG produced by the enterocyte is derived from both exogenous and endogenous lipid sources (11–14). However, the concept of a pharmaceutically relevant quantity of long-chain lipid administered in the fasted state being able to induce endogenous TG transport as a contributing basis to lymphatic transport of a drug in a human-relevant animal model such as the dog has not previously been reported. Further studies are currently being undertaken to explore the basis and selectivity of the apparent ability of exogenous lipid to either stimulate or enhance exogenous lipid transport.

The mean maximum concentration of Hf within lymph after fasted administration of the long-chain formulation was approximately 10-fold higher (106 μg/ml) than that observed

Table I. Summary Pharmacokinetic Parameters and Lymphatic Transport Data of Halofantrine after Oral Administration to Fed and Fasted Dogs

Formulation[a] (fasted or fed administration)	Plasma pharmacokinetics				Lymphatic transport (0–10 h)			
	Dose (Hf base)	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-10h} (ng·h/ml)	Cumulative Hf dose (%) in lymph	Maximum [Hf] in lymph (μg/ml)	Maximum Hf per mg lymph TG (μg Hf/mg TG)	Cumulative mass of lymph TG (g)
ME-LC (fasted)	1.6 mg/kg[b]	102 ± 5.1	3.0 ± 0.6	550 ± 147	28.3 ± 7.6	106 ± 32.2	12.29 ± 4.03	3.4 ± 2.2
ME-MC (fasted)	1.6 mg/kg[b]	59.1 ± 21.0[c]	2.7 ± 0.6	372 ± 116	5.00 ± 0.95[c]	8.7 ± 2.3[c]	5.14 ± 2.15[c]	0.9 ± 0.2[d]
PEG melt (fasted)[e]	3.2 mg/kg[f]	154 ± 52.8	3.4 ± 0.8	972 ± 382	1.3 ± 0.7	13.1 ± 4.5	4.81 ± 1.25	0.5 ± 0.4
PEG melt (fed)[e]	3.2 mg/kg[f]	124 ± 2.7	1.3 ± 0.5	562 ± 42.2	53.9 ± 8.2	241 ± 74.4	6.21 ± 1.40	32.6 ± 4.6
ME-LC (fasted)[g]	3.0 mg/kg[h]	704 ± 308	2.3 ± 0.5	3498 ± 1447	NA[i]	NA	NA	NA
ME-MC2 (fasted)[g]	3.0 mg/kg[h]	374 ± 198	4.2 ± 1.5	2265 ± 1128	NA	NA	NA	NA

[a] All data are mean ± SD (n = 4) except ME-MC fasted and PEG melt fasted where n = 3. The current study data are for the long-chain microemulsion (ME-LC) and the medium-chain microemulsion formulations (ME-MC). Comparative pharmacokinetic and lymph transport data are reproduced from references 6 and 9.

[b] 50-mg dose administered to greyhounds with an average weight of 31.5 kg.

[c] Two-sample *t* test, $p < 0.05$ for ME-MC formulation versus ME-LC formulation.

[d] Two-sample *t* test, $p < 0.1$ for ME-MC formulation versus ME-LC formulation.

[e] Data reproduced from ref. 6; the lipid-free PEG melt was an amorphous PEG 6000 solid dispersion prepared by the fusion method as described in ref. 19.

[f] 100-mg dose administered to greyhounds with an average weight of 31.5 kg.

[g] Data reproduced from ref. 9. The long-chain microemulsion (ME-LC) was identical to the formulation administered in the current study. The medium-chain microemulsion (ME-MC2) differed slightly in the proportions of the components present and consisted of 50 mg Hf, 333 mg Captex 355, 167 mg Capmul MCM, 350 mg Cremophor EL, and 100 mg ethanol per 1 g of formulation. The absolute bioavailability of Hf after oral administration of these formulations to beagle dogs was 67.3% and 52.7% after administration of the long-chain microemulsion (ME-LC) and medium-chain microemulsion (ME-MC2), respectively (9).

[h] 50-mg dose administered to beagles with an average weight of 16.5 kg.

[i] NA, not applicable; these studies were conducted in intact dogs (i.e., not lymph-cannulated).

with the medium-chain formulation (8.7 μg/ml), and this is consistent with the long-chain formulation having the apparent ability to initiate and then support lymphatic transport. Importantly, on a dose-normalized basis, the maximum Hf lymph concentration after fasted administration of the long-chain formulation was similar to that obtained after postprandial administration of the lipid-free PEG melt formulation (Table I). The concentration of Hf per milligram of lymphatically transported TG after fasted administration of the long-chain formulation was a surprisingly high value of 12.29 μg/mg, which is approximately 25% of the saturated solubility of Hf in a long-chain TG. The lower concentration of Hf per milligram of lymphatically transported TG after postprandial administration, in spite of higher absolute lymphatic transport of Hf, is a consequence of the increased mass of TG transport, which effectively "diluted" the concentration of Hf present.

In quantitative terms, the maximum concentration of Hf in lymph after fasted administration of the long-chain formulation was several orders of magnitude higher than the maximal Hf plasma concentrations previously observed after administration of similar formulations to intact (i.e., noncannulated) beagle dogs (Table I). The observation of high drug concentrations in lymph has important drug delivery and pharmacokinetic implications, especially for drugs that have activity within the lymphatic system or where high drug concentrations emptying into the systemic circulation from the thoracic duct may have clinical implications. For example, it is possible that high Hf lymph concentrations may be a contributing factor to the observed postprandial prolongation of the QTc interval that has been observed in some patients (15).

The rates of intestinal lymphatic transport of Hf and TG after fasted oral administration of the medium- and long-chain formulations are shown in Figs. 2A and 2B, respectively. Although administration of the long-chain lipid formulation resulted in greater transport of Hf and TG, the maximal rate of Hf transport was coincident with the formulation-dependent maximal TG transport rates arising from administration of the long- or medium-chain formulations. The coincident transport of Hf and TG is consistent with previous studies (6,16) and supports the contention that lymphatic drug transport is highly dependent on the formation of enterocyte-derived triglyceride-rich lipoproteins.

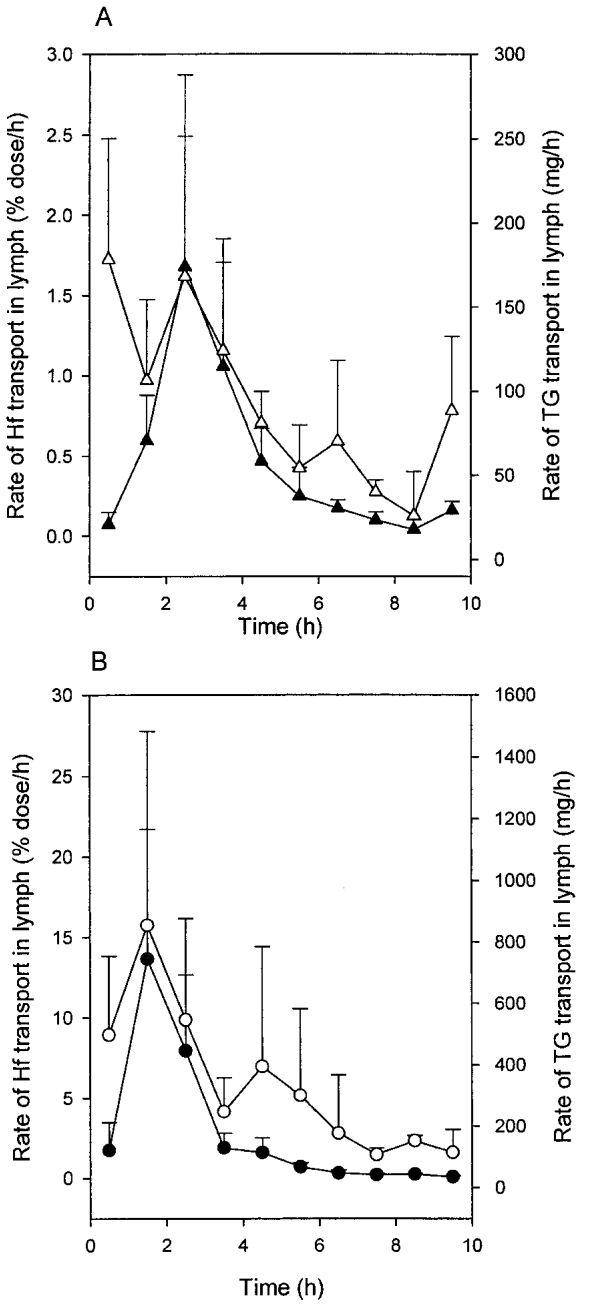

Fig. 2. Rate of lymphatic transport of halofantrine (closed symbols, expressed as percent Hf dose transported per hour) and triglyceride (open symbols, expressed as mg triglyceride per hour) after fasted administration of either a medium-chain (▲, mean ± SD, n = 3, A) or a long-chain microemulsion formulation (●, mean ± SD, n = 4, B) containing 50 mg Hf base to thoracic lymph duct–cannulated dogs.

Absorption of Halofantrine via the Portal Blood

The systemic plasma concentration vs. time profiles of Hf after fasted oral administration of the medium- and long-chain formulations to thoracic lymph duct–cannulated dogs are presented in Fig. 3 and Table I. Systemic plasma concentrations measured in this study represent drug absorption via the portal blood route because the lymphatic contribution has been removed via cannulation of the thoracic lymph duct. Although a trend toward increased C_{max} and $AUC_{0\text{-}10h}$ values for Hf after administration of the long-chain formulation compared with the medium-chain formulation was observed, the limited size of the study precludes attainment of statistical significance.

In a previous Hf bioavailability study conducted in non-lymph-cannulated fasted beagles with similar long-chain and medium-chain formulations (9), the plasma Hf concentration profiles were approximately three-fold higher than that observed in the current study using lymph-cannulated dogs (presumably reflecting the contribution of lymphatic transport to systemic plasma levels in the non-lymph-cannulated animals), and there was a clear trend to higher oral bioavailability from the long-chain compared with the medium-chain formulation (Table I). The current results suggest that the previously observed higher oral bioavailability of Hf from the long-chain formulation, compared with the medium-chain formulation, most likely reflected drug absorption via the lymphatics and

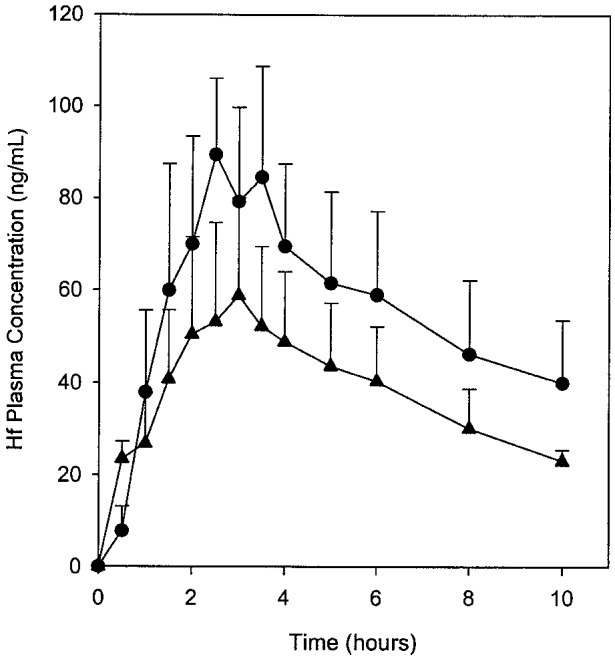

Fig. 3. Systemic plasma concentration versus time profile of halofantrine (Hf) after fasted oral administration of 50 mg Hf base formulated in either a long-chain (●, mean ± SD, n = 4) or a medium-chain microemulsion formulation (▲, mean ± SD, n = 3) to thoracic lymph duct–cannulated dogs.

portal blood, whereas the medium-chain formulation was likely capable of supporting absorption only via the portal blood.

CONCLUSIONS

This study demonstrates that small, pharmaceutically relevant volumes of appropriately formulated lipid can surprisingly initiate and support the lymphatic transport of Hf after fasted administration to dogs. Long-chain lipids resulted in greater enhancement of intestinal lymphatic TG and Hf transport than did medium-chain lipids, and this appeared to be a result of the ability of long-chain lipids to stimulate the endogenous production of TG, thereby providing enhanced intestinal lipoprotein formation to support coincident drug transport. These results suggest that promotion of intestinal lymphatic transport is possible for appropriately lipophilic drugs after fasted administration in relatively standard lipid-based dose forms and that postprandial administration in not required to promote intestinal lymphatic drug transport.

Because the apparent stimulation of intestinal lymphatic transport in the fasted state was dependent on the fatty acid chain length, this may have important implications (a) when assessing the absorption of lipophilic drugs administered in a partial-prandial state, (b) during safety assessment of new drug candidates when lipid-based approaches are used to enhance drug exposure, (c) when assessing the activity and safety profiles of highly lipophilic drugs in humans (and especially those drugs with potential QTc liabilities), and (d) when assessing altered pharmacokinetic and activity/safety profiles of highly lipophilic drugs in regard to changed distribution and clearance profiles as a consequence of lymphatic transport (17,18).

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