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Targeted lymphatic transport and modified systemic distribution of CI-976, a lipophilic lipid-regulator drug, via a formulation approach

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Abstract

CI-976 is a poorly water soluble lipid regulator with good solubility in triglycerides and a high octanol:water partition coefficient. These physicochemical properties suggest significant lymphatic transport following gastrointestinal absorption. Studies were conducted to assess the relative contribution of lymphatic transport to total systemic bioavailability. Following intraduodenal administration to conscious rats as either a 20% o/w emulsion prepared from a mixture of soybean and safflower oils, or as an aqueous suspension, the percentage contribution of lymphatic transport to bioavailability as reflected by CI-976 plasma AUC was 43% for the emulsion and 57% for the suspension. However, the total quantity of CI-976 transported in lymph over 14 h, as a percent of dose administered, was 7-times greater for the emulsion as compared to the suspension. Tissue distribution studies using [^{14}C]CI-976 showed that, compared to the suspension, the emulsion delivery system resulted in 43% greater accumulation of intact CI-976 in the perirenal fat. Enhanced lymphatic transport is not necessarily reflected by a proportionally elevated plasma AUC, therefore plasma AUC alone may not be representative of total systemic bioavailability of drug.

Key words: Lymphatic transport; Drug delivery; Drug distribution; Drug targeting; ACAT inhibitor; Emulsion; Chylomicron; Lymph

1. Introduction

Gastrointestinal absorption of drugs may occur via the hepatic portal system, through lymphatic uptake via the lacteals, or by a combination of both pathways. Highly lipophilic drugs possessing good solubility in triglycerides are potential candidates for significant lymphatic transport (Charman and Stella, 1991). DDT, a model compound for studying lymphatic transport, has a log P of 6.19 and approx. 100 mg/ml solubility in peanut

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oil and shows 33.5% cumulative lymph transport in rats administered a 10 mg oral dose (Stella et al., 1990). Association of drugs with chylomicrons constitutes an important means of drug entry into the lymphatic circulation. Chylomicrons are triglyceride-rich lipoproteins synthesized by the enterocyte in response to lipid digestion and absorption. Chylomicrons range from 50 to 500 nm in diameter and consist of a triglyceride core surrounded by a monolayer of polar phospholipids and apoproteins. Chylomicrons serve to solubilize hydrophobic triglyceride in the predominantly aqueous environment of the blood and to regulate its movement into specific target cells and tissues. Drug delivery vehicles containing fatty acids C_{16} to C_{18} in chain length stimulate chylomicron synthesis and can enhance lymphatic transport of coadministered drugs (De Nijs, 1987). Following exocytosis of the drug-laden chylomicrons into the lamina propria, selective uptake into the lymphatic vessels occurs via size exclusion (De Nijs, 1987). Blood vessels, unlike lymphatic channels, possess a basement membrane which inhibits passage of the relatively large chylomicrons. Drugs absorbed via the intestinal lymphatics enter the central blood circulation at the juncture of the left internal jugular vein and subclavian vein without passing through the liver, thus avoiding first-pass inactivation through hepatic metabolism. Once in the central blood circulation, chylomicrons are rapidly cleared with an approximate half-life of less than 3 min in the rat (Kilian, 1973). The clearance is mediated primarily by the action of lipoprotein lipase, located in the peripheral adipose tissue. This enzyme hydrolyzes the chylomicron core triglyceride into free fatty acids, which are then transferred to the adipose tissue, and results in the formation of a chylomicron remnant consisting of the phospholipid shell and apoproteins contained in the former chylomicron (Kortz et al., 1984; Guyton, 1986). Chylomicron remnants are actively and preferentially cleared from the blood by the liver (Drevon, 1991). A drug associated with one or more of the lipid components present in chylomicrons may follow these lipid components in their distribution throughout the body, causing the drug distribution to be altered by a delivery system

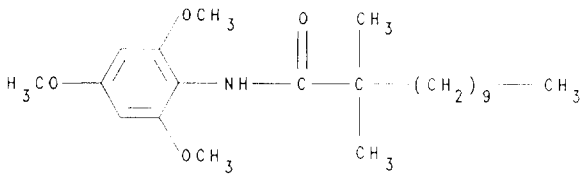

Fig. 1. CI-976 (2,2-dimethyl-*N*-[2,4,6-trimethoxyphenyl] dodecanamide.

that enhances lymphatic transport. CI-976 (Fig. 1), a trimethoxyanilide of 2,2-dimethyldodecanoic acid, is a lipid regulator which competitively inhibits the enzyme, acyl-CoA:cholesterol acyltransferase (ACAT). ACAT catalyzes esterification of cholesterol within intestinal mucosal cells and arterial intima and consequently is important in cholesterol absorption as well as accumulation in arteries (Bocan et al., 1991). The compound has an octanol/water log P of 5.83, corn oil solubility of > 100 mg/ml, and is practically insoluble in water (1.1 μg/ml). These physicochemical properties are compatible with those necessary for significant lymphatic transport following gastrointestinal absorption (Stella and Charman, 1989). The objectives of this study were to: (1) investigate the effect of the dosage form on the lymphatic transport of CI-976; (2) determine the relative contribution of the lymphatically transported CI-976 to the plasma AUC for both dosage forms; (3) investigate the effect of the dosage form on the distribution of CI-976 to liver and adipose tissues.

2. Materials and methods

2.1. Chemicals

CI-976 and [^{14}C]CI-976 were synthesized by Parke-Davis Pharmaceutical Research, Division of Warner Lambert Co. (Ann Arbor, MI, U.S.A.). Isopropanol, methanol, acetonitrile, and water were all obtained as HPLC grade from Fisher Scientific (Fairlawn, NJ, U.S.A.). Blank plasma and mesenteric lymph were collected from fasted male Wistar rats. All other chemicals were reagent grade unless otherwise specified.

2.2. Animals

Male Wistar rats were purchased from Acc Animals (Boyertown, PA, U.S.A.) and maintained on Agway ProLab RMH 1000 animal diet and water ad libitum. The housing environment was maintained at 65–75°F with an air exchange rate of 10 changes per h. The animals were exposed to a 12 h light-dark cycle.

2.3. Emulsion formulation

A 20% lipid emulsion of CI-976 was prepared by dissolving 5 g of CI-976 in 40 g of a mixture of equal parts of Refined Soybean Oil, USP and safflower seed oil. The oil phase was heated to 80°C. Egg yolk lecithin (Sigma type XV-E) 2.4 g, was dispersed in 140 ml of deionized water with 5 g of glycerol and heated to 80°C. The oil phase was combined with the aqueous phase, brought to 200 ml total volume with deionized water heated to 80°C, and homogenized at 15000 rpm on a Polytron® PT3000 homogenizer for 5 min. The resulting coarse dispersion was passed through a Microfluidics® M110F microfluidizer four times using a system operating pressure of 80 psig. The final concentration of CI-976 in the emulsion was 25 mg/ml.

2.4. Aqueous suspension formulation

Micronized CI-976 (average particle size, 5 μm) was suspended in an aqueous dispersion of Avicel® RC-591 (1% w/v) and CMC sodium USP Type 7 MF (0.5% w/v). Polysorbate 80 (0.2% w/v) and glycerin (4% w/v) were incorporated as wetting agents. Sodium benzoate (0.5%) was included as a preservative and citric acid was added to adjust the pH to 5. The formulation also included sucrose (30% w/v). The final concentration of CI-976 in the formulation was 50 mg/ml.

2.5. Red blood cell : plasma partitioning and protein binding

Aliquots of 450 μl of rat whole blood were spiked with 50 μl of appropriate concentrations of CI-976 in methanol to give final blood concentrations ranging from 0.5 to 10 μg/ml. The blood samples were vortexed for 30 s following addition of the spiking solutions. A 100 μl aliquot of the blood was prepared for HPLC analysis as previously described (Hauss et al., 1993). The remaining blood samples were centrifuged at $16000 \times g$ for 10 min and the plasma collected. Aliquots of 100 μl of plasma were analyzed for CI-976 concentration as described above. The red blood cell concentration of CI-976 was calculated (Eq. 1) from the whole blood and plasma concentrations and the hematocrit, which is 0.448 for rat whole blood (Myers and Stella, 1992).

$$\{\text{Blood concentration} - \{\text{plasma concentration} \times (1 - \text{hematocrit})\}\}/(\text{hematocrit}) \quad (1)$$

The remaining plasma samples were placed in an ultrafiltration device (model MPS-1 with YMT membrane, Amicon, Danvers, MA) and centrifuged at 2000 rpm for 60 min at 37°C. A 25 μl aliquot of the filtrate was directly injected onto the HPLC column and analyzed for CI-976.

2.6. Surgical procedures

In control rats, drug absorbed from the gastrointestinal system enters the central blood circulation via direct absorption into the portal circulation and indirectly, following transport into the lymph. Thus, both lymphatically transported drug and drug absorbed via the portal should route contribute to overall plasma AUC. In rats cannulated for the collection of mesenteric lymph, only the drug absorbed into the portal circulation contributes to the overall plasma AUC. Assessment of the contribution of lymphatically transported CI-976 to overall plasma AUC was done by comparing the CI-976 plasma AUC of control rats to those in which the mesenteric lymph duct was cannulated for the collection of lymph. Orally administered lipids delay gastric emptying and increase GI residence time of co-administered drugs, often resulting in an increase in bioavailability. To eliminate the effect of this variable when comparing the relative bioavailability of CI-976 from the lipid emulsion and aqueous suspension, the formulations were administered via a

duodenal cannula. Male Wistar rats, 225–250 g in weight, were anesthetized by an intraperitoneal injection of 65 mg/kg of sodium pentobarbital. The right external jugular vein and duodenum of all rats were cannulated with 0.02 inch i.d. silastic tubing. For collection of lymph, the mesenteric lymph duct was cannulated with PE 50 tubing. Since lymphatic cannulation was accomplished through the same abdominal wound as the duodenal cannulation, non-lymph-cannulated animals were considered sham operated. The animals were transferred to restraining cages and a continuous infusion of normal saline was begun via the jugular cannula (2 ml/h for lymph cannulated rats, 0.9 ml/h for non-lymph cannulated rats). Animals producing less than 2 ml/h of lymph were excluded from the study. Following an overnight recovery, 1 ml of either the aqueous suspension or the lipid emulsion was introduced as a bolus via the duodenal cannula. 250 μl aliquots of blood were withdrawn from the jugular cannula at 0.25, 0.50, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, and 14 h and placed in heparinized polypropylene centrifuge tubes. Blood samples were immediately centrifuged and the plasma was collected and prepared for HPLC assay. Total lymph volume was collected between blood sampling intervals into 20 ml glass scintillation vials containing 20 IU of heparin sodium.

2.7. Drug distribution studies

The effect of the formulation on the distribution of CI-976 between the liver and perirenal fat was determined using [^{14}C]CI-976. Labelled suspension or emulsion formulations were prepared by adding 50 μl aliquots (25 μCi) of a solution of [^{14}C]CI-976 in absolute ethanol to 1 ml of either the emulsion or suspension. The mixtures were then vortexed vigorously for 30 min prior to administration. This technique has been used sucessfully in our laboratory to incorporate CI-976 into the lipid phase of the commercially prepared intravenous fat emulsion, Liposyn®. Following addition to the suspension, the labelled CI-976 distributes between the suspended solid and solubilized CI-976 phases in a proportion similar to the unlabelled drug. Duodenal cannulae were implanted as described under section 2.6. Following an overnight fast, the animals were administered, via the duodenal cannula, 1 ml of the labelled CI-976 suspension or emulsion. After 13 h, the animals were killed by cervical dislocation and the liver and perirenal fat rapidly removed. Both liver and fat were rinsed three times with 20 ml of ice-cold saline and blotted between paper towels after each rinse. The liver was then weighed, ice-cold distilled water added to make a 25% w/w suspension, and homogenized over ice with a Polytron® PT3000 homogenizer. Fat tissue was treated similarly, except homogenization was performed in methanol at room temperature. To prepare liver tissue for liquid scintillation counting, 2 gm of the homogenate was added to 2 ml of Scintigest® tissue solubilizer (Fisher Scientific, Malvern, PA) and placed in a shaking water bath for 16 h at 50°C. The digested sample was decolorized with 0.5 ml of 35% hydrogen peroxide, neutralized with 1.5 ml of 0.5 N HCl, and 13.5 ml of Scintiverse® BD liquid scintillation cocktail added (Fisher Scientific, Malvern, PA). Fat homogenate was prepared for liquid scintillation counting by centrifugation and addition of 1 g of the supernatant to 20 ml of Scintiverse® BD. All samples were vortexed, allowed to stand overnight at 4°C in the dark, and counted on a Packard Tricarb scintillation counter. Results were calculated as DPM using quench curves prepared from similarly treated control tissues.

2.8. HPLC assay methodology for plasma and mesenteric lymph

A validated HPLC method was used for quantitation of CI-976 in rat plasma and lymph (Hauss et al., 1993). For radiochromatographic analysis of fat and liver samples, HPLC conditions for CI-976 in lymph were used. Fat samples were prepared by centrifuging 1 ml aliquots of the methanol homogenates and directly injecting the supernatants onto the HPLC column. Liver homogenates were prepared by extracting 1 ml volumes of homogenate with 3 ml of methanol and processing as described above for lymph and plasma (Hauss et al., 1993). The methanol extracts were evaporated at 60°C under reduced

pressure, reconstituted to one-quarter the original volume with isopropanol/acetonitrile/water (153:153:94), and injected directly onto the HPLC column. Radioactivity in liver and fat samples associated with intact CI-976 is expressed as the percentage peak area of total radioactivity in CPM eluting at the same time as the unlabeled drug molecule.

2.9. Pharmacokinetic analysis of data

Pharmacokinetic parameter values were estimated by non-compartmental analysis of individual rat plasma CI-976 concentration-time data. Apparent terminal phase elimination rate constant values were estimated as the value of the slope of the least-squares linear regression of the terminal phase of the natural logarithmic plasma CI-976 concentration-time profiles. Area under plasma CI-976 concentration-time curve (AUC) values were estimated from 0 to 14 h using the linear trapezoidal method. Comparison of means was performed using a one-sided Student's *t*-test.

3. Results and discussion

3.1. Red blood cell: plasma partitioning and protein binding

To ascertain that plasma CI-976 levels were reflective of whole blood CI-976 concentrations, studies were undertaken to assess the partitioning of CI-976 between plasma and red blood cells.

Table 1
CI-976 red blood cell: plasma concentration ratios

CI-976 blood concentration (μg/ml)	Concentration of CI-976 in methanol (μg/ml)	Assayed blood concentration (μg/ml)	Assayed plasma concentration (μg/ml)	Calculated RBC concentration (μg/ml)	CI-976 RBC: plasma concentration ratio
0.5	5	0.31	0.2	0.45	2.25
1	10	0.78	0.74	0.84	1.13
2	20	1.36	1.57	1.11	0.71
5	50	4.54	4.38	4.74	1.08
10	100	9.66	8.89	10.60	1.19

Table 2
Pharmacokinetic parameters determined for CI-976 in fasted male Wistar rats following intraduodenal administration of an aqueous suspension and a lipid emulsion

	Animal no.	AUC (μg h ml^{-1})	C_{max} (μg/ml)	t_{max} (h)	CI-976 in lymph (μg) (0–14 h)	% of dose in lymph (0–14 h)
Suspension (222 mg/kg)	1	13.71	1.41	4	9.53	0.02
	2	26.85	2.42	4	39.02	0.08
	3	19.39	1.87	4	32.91	0.07
Suspension (control)	1	67.64	6.67	2	–	–
	2	38.55	5.71	0.5	–	–
	3	34.39	3.62	2	–	–
Emulsion (111 mg/kg)	1	11.52	1.54	0.75	130.54	0.52
	2	11.95	1.59	2	29.54	0.12
	3	10.26	1.65	0.75	137.08	0.55
Emulsion (control)	1	16.47	1.89	0.75	–	–
	2	18.39	2.00	4	–	–
	3	23.77	2.68	4	–	–

The results indicate that the distribution of CI-976 between red blood cells and plasma is similar over the concentration range seen in this study (Table 1). The CI-976 concentrations in the ultrafiltrates were below the limit of quantitation for all concentrations studied, indicating a very high degree of association of CI-976 with plasma proteins.

3.2. Emulsion

In non-lymph cannulated rats, mean plasma AUC ($n = 3$) from 0 to 14 h following duodenal administration of 1 ml of the 25 mg/ml emulsion (111 mg/kg) was 19.54 μg h ml^{-1} (RSD 19%). The mean elimination half-life was 11.9 h. In lymph cannulated rats, mean plasma AUC ($n = 3$) was 11.24 μg h ml^{-1} (RSD 8%), and the average cumulative amount of CI-976 absorbed by mesenteric lymph over 14 h was 99 μg (RSD 61%), which represented 0.40% of the dose (Table 2, Fig. 2). The difference in CI-976 plasma AUC values was significant at the $p < 0.025$ level. Average lymphatic contribution to total CI-976 plasma AUC was 43% (Fig. 3). An examination of the individual plasma concentration-time profiles revealed that cannulation for collection of mesenteric lymph resulted in elimination of the double peak characteristic in the non-cannulated plasma concentration-time profiles (Fig. 4a,b). While the amount of CI-976 transported into lymph was variable, the times during which the double peak occurred (2–4 h) fell within the time interval during which rate of transport was maximal (0.5–6 h) (Fig. 2). The absence of double-peaking in the plasma concentration-time profiles of lymph cannulated animals is suggestive of the possibility that the double-peak phenomenon seen in this instance is due to the delayed entry of lymphatically absorbed drug into the blood circulation.

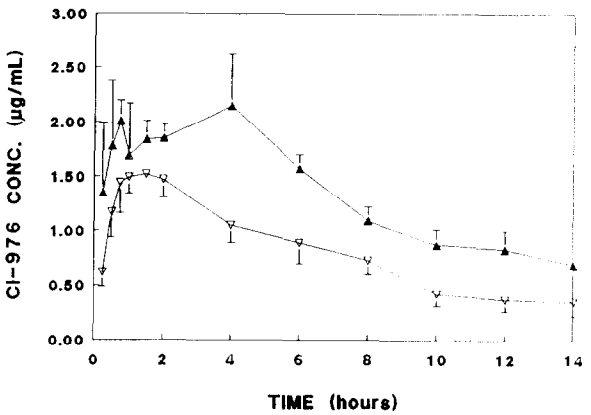

Fig. 3. CI-976 plasma concentration-time profile in rats following intraduodenal administration of 25 mg of CI-976 as a lipid emulsion with mesenteric lymph duct intact (▲) and cannulated (▽) (data points represent means ± S.D., $n = 3$).

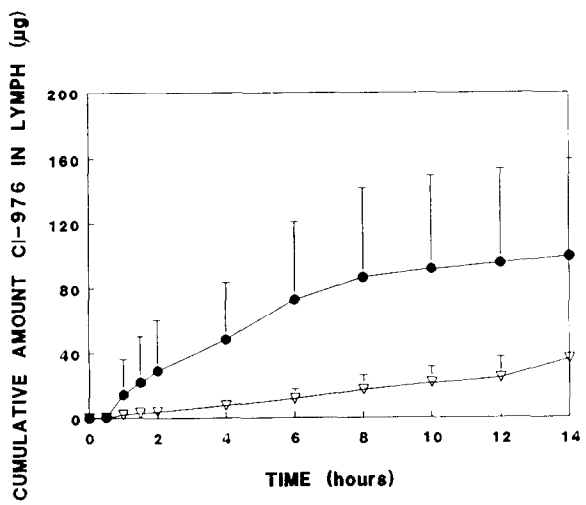

Fig. 2. Cumulative transport of CI-976 into mesenteric lymph vs time following intraduodenal dosing of 25 mg of CI-976 as an emulsion (●) or 50 mg of CI-976 as an aqueous suspension (▽) (data points represent means ± S.D., $n = 3$).

3.3. Aqueous suspension

In non-lymph cannulated rats, mean plasma AUC ($n = 3$) from 0–14 h following duodenal administration of 1 ml of the 50 mg/ml suspension (222 mg/kg) was 46.86 μg h ml^{-1} (RSD 39%). The mean elimination half-life was 9.1 h. In lymph cannulated rats, mean plasma AUC ($n = 3$) was 19.98 μg h ml^{-1} (RSD 33%). The difference in the CI-976 plasma AUC values was significant at the $p < 0.05$ level. The average cumulative amount of CI-976 absorbed by mesenteric lymph over 14 h was 27 μg (RSD 57%) which represented 0.06% of the dose (Fig. 2).

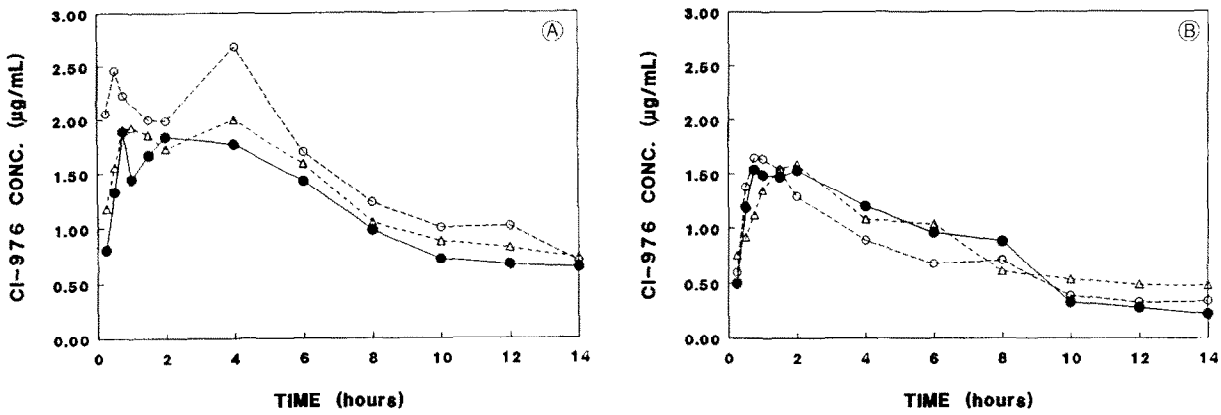

Fig. 4. (a) Individual plasma concentration-time profiles in rats following intraduodenal administration of 25 mg of CI-976 as a lipid emulsion (intact mesenteric lymph duct). (b) Individual plasma concentration-time profiles in rats following intraduodenal administration of 25 mg of CI-976 as a lipid emulsion (cannulated mesenteric lymph duct).

Average lymphatic contribution to total CI-976 plasma AUC was 57% (Fig. 5). Occurrence of double peaks in the individual plasma concentration-time profiles was not as uniform as that seen with the emulsion dosage form (Fig. 6a,b). The reasons for this are not clear. However, the absence of co-administered triglyceride would result in significantly lesser chylomicron flux than that seen with the emulsion. Presumably, the contribution of the chylomicron pathway to lymphatic transport of CI-976 would be reduced. Other pathways, such as passive diffusion into the lymph from the interiors of the absorptive intestinal cells, or association with very low density lipoprotein (VLDL), would then play a relatively larger role in the lymphatic transport of CI-976 (Stella and Charman, 1989). The kinetics of these processes are different from those of chylomicron transport, and the expected result would be a different time course of appearance, in the plasma, of lymphatically transported CI-976.

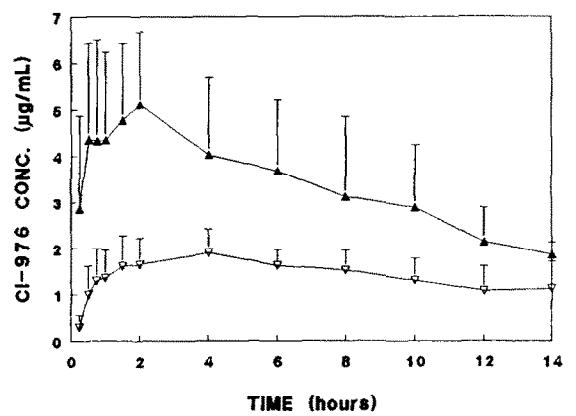

Fig. 5. CI-976 plasma concentration-time profile in rats following intraduodenal administration of 50 mg of CI-976 as an aqueous suspension with mesenteric lymph duct intact (▲) and cannulated (▽) (data points represent means ± S.D., $n = 3$).

3.4. Influence of drug delivery system on tissue distribution of CI-976

Comparison of the total radioactivity found in fat and liver tissue 13 h post-dose for the aqueous suspension and lipid emulsion dosage forms spiked with [^{14}C]CI-976 showed that the lipid emulsion resulted in the accumulation of 43% more radioactivity, as intact CI-976, in the perirenal fat ($p < 0.01$, $n = 6$) (Fig. 7). These results indicate that when CI-976 is dosed in a lipid emulsion which promotes lymphatic transport, a greater portion of CI-976 is directed to the adipose tissue, as compared to when the compound is dosed in an aqueous suspension. The enhanced lymphatic transport of CI-976 seen with the lipid emulsion was not correlated with a significant increase in CI-976 transport to the liver. This may indicate that CI-976 is transported in the triglyc-

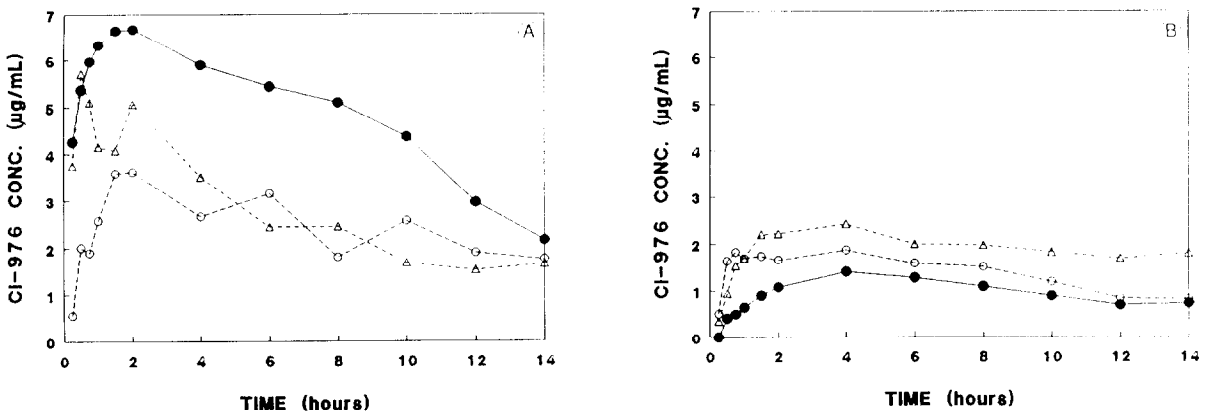

Fig. 6. (a) Individual plasma concentration-time profiles in rats following intraduodenal administration of 50 mg of CI-976 as an aqueous suspension (intact mesenteric lymph duct). (b) Individual plasma concentration-time profiles in rats following intraduodenal administration of 50 mg of CI-976 as an aqueous suspension (cannulated mesenteric lymph duct).

eride core of the chylomicron, which is assimilated by the peripheral adipose tissue, and is consistent with the high triglyceride solubility of the compound (Kilian, 1973). Had CI-976 associated preferentially with the phospholipid shell of the chylomicron, enhanced lymphatic transport of CI-976 would be expected to result in increased liver levels of compound due to the preferential uptake of chylomicron remnants by the liver (Drevon, 1991). While the contribution of lymphatically absorbed CI-976 to plasma AUC is significant and similar for both aqueous suspension and lipid emulsion delivery systems, the percent of the dose administered which was transported via the lymph was 7-times greater for the emulsion. The lack of a proportionally greater

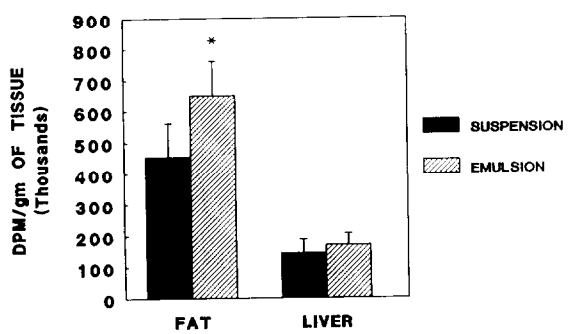

Fig. 7. Total radioactivity in perirenal fat and liver tissue following intraduodenal administration of CI-976 as the lipid emulsion or aqueous suspension, spiked with 25 μCi of [^{14}C]CI-976 (data represent means ± S.D., $n = 6$; (*) = significant at $p < 0.01$).

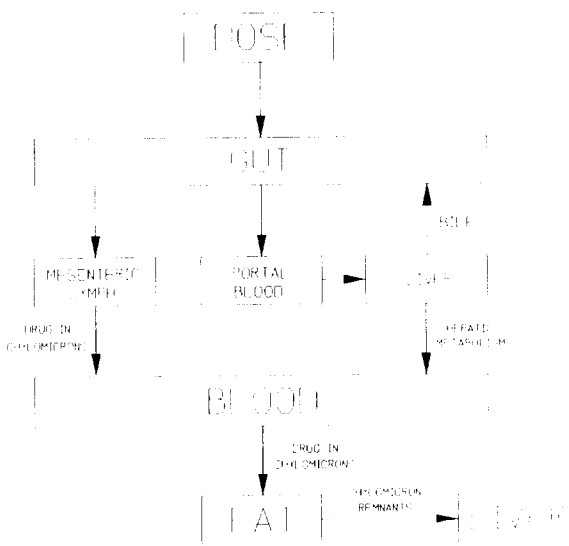

Fig. 8. Schematic illustration showing fate of orally dosed CI-976 in an emulsion delivery system and blood clearance of chylomicrons containing CI-976 by the adipose and liver tissues.

contribution to plasma AUC of lymphatically absorbed CI-976 from the emulsion delivery system may be attributed to the rapid redistribution of CI-976, in the chylomicrons, from the central compartment into the fat (Fig. 8). This hypothesis is supported by the drug distribution studies which show that the lipid emulsion delivery system results in significantly greater accumulation of CI-976 in the adipose tissue.

4. Conclusion

The results of these studies indicate that, for a lipophilic compound such as CI-976, lymphatic transport significantly contributes to plasma drug concentration time profiles, irrespective of the type of the dosage form. In this study, double-peaking in the plasma concentration-time profiles following emulsion dosing appeared to be the result of the appearance of lymphatically transported CI-976 in the plasma. In addition, gastrointestinal administration of CI-976 in a lipid emulsion delivery system results in increased lymphatic transport of drug, resulting in significantly higher concentrations of drug in the adipose tissue. However, the increased lymphatic transport of CI-976 did not result in a proportionate increase in CI-976 plasma AUC. Practical implications of these findings to scientists involved in the design and evaluation of drug delivery systems are: (1) administration of lipophilic drugs in emulsion-type vehicles incorporating fatty acids C_{16} to C_{18} in chain length, which stimulate chylomicron production, may enhance drug levels in the lymph and result in targeting of greater amounts of drug to the adipose tissue; (2) plasma concentration-time data alone may not fully reflect relative bioavailability and pharmacodynamic potential of lipophilic drugs dosed in emulsion-type vehicles.

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References

Bocan, T.A., Mueller, S.B., Uhlendorf, P.D., Newton, R.S. and Krause, B.K., Comparison of CI-976, an ACAT inhibitor, and selected lipid-lowering agents for antiatherosclerotic activity in iliac-femoral and thoracic aortic lesions. *Arteriosclerosis Thromb.*, 11 (1991) 1830–1843.

Charman, W.N.A. and Stella, V.J., Transport of lipophilic molecules by the intestinal lymphatic system. *Adv. Drug Del. Rev.*, 7 (1991) 1–14.

De Nijs, H., Targeting of drugs to the lymph. *Acta Pharm. Technol.*, 33 (1987) 163–168.

Drevon, C.A., Absorption, transport and metabolism of vitamin E. *Free Radical Res. Commun.*, 14 (1991) 229–246.

Guyton, A.C., *Textbook of Medical Physiology*, W.B. Saunders, Philadelphia, 1986, pp. 818–819.

Hauss, D.J., Martin, P.J., Mehta, S.C. and Radebaugh, G.W., The determination of 2,2-dimethyl-*N*-(2,4,6-trimethoxyphenyl dodecanamide, a lipid regulator, in rat plasma and mesenteric lymph by reversed-phase high performance liquid chromatography. *J. Chromatogr. Biomed. Appl.*, 613 (1993) 336-339.

Kilian, H., Participation of the lymphatic system in the absorption of pharmaca from the gut. Dissertation, University of Nijmegen, The Netherlands, 1973, p. 109.

Kortz, W.J., Schirmer, B.D., Mansbach, C.M., II, Shelburne, F., Toglia, M.R. and Quarfordt, S.H., Hepatic uptake of chylomicrons and triglyceride emulsions in rats fed diets of differing fat content. *J. Lipid Res.*, 25 (1984) 799–804.

Myers, R.A. and Stella, V.J., Factors affecting the lymphatic transport of penclomedine (NSC-338720), a lipophilic cytotoxic drug: Comparison to DDT and hexachlorobenzene. *Int. J. Pharm.*, 80 (1992) 51–62.

Stella, V.J. and Charman, W.N.A., Intestinal lymphatic transport of lipophilic molecules. In Prescott, L.F. and Nimmo, W.S. (Eds), *Novel Drug Delivery and its Therapeutic Application*, Wiley, London, 1989, pp. 57–68.

Stella, V.J., Charman, W.N.A. and Myers, R.A., Targeting of orally administered lipophilic drugs to the lymphatic system. *Proc. Int. Symp. Controlled Release Bioact. Mater.*, 17 (1990) 184–5.