Lymphatic Transport of Methylnortestosterone Undecanoate (MU) and the Bioavailability of Methylnortestosterone Are Highly Sensitive to the Mass of Coadministered Lipid after Oral Administration of MU


Drug Delivery Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), Parkville, Victoria, Australia (K.L.W., G.N., W.N.C., C.J.H.P.); Department of Veterinary Sciences, the University of Melbourne, Werribee, Victoria, Australia (G.A.E.); and Department of Pharmaceutics, Schering-Plough, Oss, The Netherlands (W.A.F.)

Received May 21, 2009; accepted August 19, 2009

ABSTRACT

The contribution of lymphatic transport to the oral bioavailability of methylnortestosterone (M) after oral administration of the lipophilic prodrug methylnortestosterone undecanoate (MU) has been evaluated, and the sensitivity of lymphatic MU transport to lymphatic lipid transport has been investigated. M and MU were administered intravenously and orally to greyhound dogs to determine absolute bioavailability after oral dosing of MU. MU was also administered orally with differing quantities of food (lipid) to lymph duct-cannulated greyhound dogs to investigate the relative roles of lymph versus blood transport on M bioavailability and the effect of lipid load on systemic exposure. The relationship between lymphatic lipid and MU transport was further investigated in anesthetized rats. The oral bioavailability of M after administration of MU was found to be highly dependent on coadministration of food, and the bioavailability of M increased approximately 700% in fed versus fasted animals. In both cases, lymph diversion resulted in negligible systemic exposure of M, indicating almost complete dependence on lymphatic transport of MU for systemic exposure of M. Lymphatic transport of MU was even more highly dependent on the quantity of coadministered lipid and increased more than 50-fold with increasing lipid load. Therefore, increasing the quantity of food or lipid coadministered with MU stimulated a significant increase in the lymphatic transport of MU and systemic exposure of M. The lipid sensitivity of lymphatic transport of MU is significantly higher than previously observed for more metabolically stable compounds, suggesting a role for coadministered lipid in promoting avoidance of enterocyte-based cleavage of MU.

7α-Methyl-19-nortestosterone (M) is a potent and selective synthetic androgen with potential for the treatment of testosterone insufficiency (Anderson et al., 2003) and control of male fertility (von Eckardstein et al., 2003). M is a more potent agonist at androgen receptors than testosterone (Kumar et al., 1999), but unlike testosterone, M is not a substrate for 5α-reduction (Agarwal and Monder, 1988; Kumar et al., 1992) and therefore is considered to be a prostate-sparing androgen. M has previously been administered as a slow-release oily depot or subdermal implant of a prodrug ester (typically the acetate) (Anderson et al., 1999; Noé et al., 1999). However, discomfort arising from implant insertion has been reported, and patient complaints that the location of the implants (medial aspect of the upper arm) interferes with normal physical activity have also been noted (Noé et al., 1999). Implants also suffer from the disadvantage that they must be surgically implanted by a medical practitioner. Therefore, an oral dosage form of M that allowed for self-administration would offer advantages in terms of patient acceptability.

Although the oral bioavailability of M has not been reported, like testosterone it is expected to be low because of extensive presystemic metabolism during transit across the gut. This study was supported by funding from Schering-Plough, Oss, The Netherlands. Article, publication date, and citation information can be found at http://pet.aspetjournals.org. doi:10.1124/jpet.109.154542.

ABBREVIATIONS: M, 7α-methyl-19-nortestosterone; TU, testosterone undecanoate; MU, 7α-methyl-19-nortestosterone undecanoate; HPLC, high-performance liquid chromatography; LC, liquid chromatography; LLQ, lower limit of quantitation; MS, mass spectrometry; C_max, maximum plasma concentration; t_max, time to reach C_max; AUC, area under the plasma concentration versus time curve; BS, bile salt; LPC, L-α-lysophosphatidylcholine; CL, clearance; V_D, apparent volume of distribution.
gut wall and on first pass through the liver. The use of prodrugs is one approach that has been used successfully to increase the oral bioavailability of highly metabolized compounds (Stella et al., 2007). In the case of testosterone, previous studies have shown that oral administration of testosterone esters may be used to facilitate effective testosterone exposure (Coert et al., 1975; Noguchi et al., 1985), and an oral formulation for the administration of testosterone undecanoate (TU) (Andriol Testocaps; Schering Plough, Kenilworth, NJ) is currently marketed in several countries. The bioavailability of testosterone after oral administration of TU is low and predominantly attributable to lymphatic transport of the lipophilic ester prodrug followed by postabsorptive cleavage to release the active testosterone (Shackleford et al., 2003). Consistent with the dependence on lymphatic TU transport for testosterone bioavailability, the systemic exposures of TU and its active metabolites testosterone and 5α-dihydrotestosterone exhibit pronounced food effects as a consequence of enhanced lymphatic transport, and exposure to all three species is significantly higher after oral administration of TU with food (Frey et al., 1979; Bagchus et al., 2003; Schnabel et al., 2007). This finding has led to the clinical recommendation that Andriol Testocaps be taken with a meal. A recent study by Schnabel et al. (2007) has further shown in humans that the exposure to TU and its metabolites is not only dependent on the presence of food but also that the lipid content of the meal plays an important role in bioavailability. However, oral testosterone therapy is limited both by the potential for androgenic prostate effects and the relatively low potency of testosterone, which necessitates the administration of large doses of TU (up to 160 mg/day). Because of its higher potency and altered metabolic profile, M may offer advantages in terms of dose and prostate-sparing capacity. Analogs to testosterone, the undecanoate ester of M (MU) exhibits oral activity, and this activity has been hypothesized to arise from lymphatic transport of the ester and subsequent systemic hydrolysis to the free M, effectively bypassing first-pass metabolism. Preliminary evidence in humans supports this hypothesis and has shown increased MU and M exposure after oral administration of MU with food (data on file, Schering Plough, Oss, The Netherlands). To this point, however, the absolute bioavailability of MU and M has not been established, and the contribution of lymphatic transport of MU after oral administration to the bioavailability of M has not been evaluated. The sensitivity of MU and M exposure to the quantity of coadministered food has also not been examined but is potentially critically important to understanding in-use variability and to the definition of labeling requirements.

In the current study, therefore, the absolute bioavailability of MU and M was evaluated in fed and fasted greyhound dogs, and the impact of coadministration with different quantities of food (lipid) on the lymphatic transport of MU was examined. The studies suggest that systemic exposure of M is almost entirely dependent on lymphatic transport of MU and that this is highly dependent on the quantity of coadministered food (lipid). Comparison with data previously reported for the lymphatically transported antimalarial halofantrine suggests that the quantity of coadministered lipid required to support lymphatic transport is compound-specific and is related (at least in part) to the enterocyte-based metabolic lability of the drug.

### Materials and Methods

#### Materials

M and MU were supplied by Schering Plough. Intralipid (10%) was purchased from Baxter Healthcare (Sydney, NSW, Australia). Castor oil, oleic acid, L-α-lysophosphatidylcholine, sodium taurocholate, and sodium taurodeoxycholate were purchased from Sigma-Aldrich (St. Louis, MO). L-α-Lauraglycol FCC was supplied by Gattefosse (Saint Priest, France). Tween 80 was purchased from BDH Chemicals (Kilsyth, VIC, Australia). Purified egg yolk lecithin (containing approximately 60% phosphatidylcholine) was supplied by Pharmacia LKB (Uppsala, Sweden). All the other chemicals were of analytical grade, and solvents were of high-performance liquid chromatography (HPLC) grade. Water was supplied from a Milli-Q (Millipore Corporation, Billerica, MA) water purification system unless otherwise specified.

#### Methods

**In Vivo Greyhound Dog Studies.** Oral and intravenous formulations of M and MU. MU for oral administration in the dog studies was formulated in soft gelatin capsules containing castor oil/Lauraglycol FCC (60:40% w/w). Each individual capsule contained approximately 80 mg of MU in 500 mg of castor oil/Lauraglycol FCC. An aliquot of MU solution was retained at the time of capsule filling for accurate measurement of the MU concentration. Capsules were weighed before and after filling to allow the mass of MU administered to be calculated.

Intralipid containing MU and M for intravenous administration to greyhound dogs were prepared via a modification of a previously described method (Shackleford et al., 2003). In brief, 22.5 mg of MU or M was dissolved in N,N-dimethylacetamide/triacetin [3:5 (v/v), 600 μL], which was added drop-wise into 20 mL of Intralipid. Incorporation was achieved by sonication the emulsion for 2 min after the addition of each drop of MU or M solution using a probe sonicator (XL-Series; Misonix, Inc., Farmingdale, NY). The emulsion was cooled throughout the incorporation/sonication process by immersion in an ice water bath. After complete addition of the MU or M solution, the concentration of MU or M was determined before and after centrifugation to determine the extent of incorporation into oil droplets. The resulting emulsions were sterilized before administration by filtration through a 0.22-μm filter (Millipore Corporation). An aliquot of the filtered emulsion was retained immediately after administration for quantification of the exact MU or M concentration at the time of dosing. Intralipid formulations were diluted at least 100-fold in acetonitrile before analysis by HPLC.

**Bioavailability and lymphatic transport studies in greyhounds.** All the surgical and experimental procedures were approved by the Institutional Animal Experimentation Ethics Committee. For studies involving the collection of lymphatic fluid, the thoracic lymph duct of healthy adult male greyhound dogs (30–41.2 kg) was cannulated under general anesthesia as previously described (Khoo et al., 2001). After surgery, dogs were allowed to recover unrestrained for approximately 16 h during which time they resumed normal ambulatory movement. An intravenous catheter was inserted into the cephalic vein immediately before drug dosing to allow for serial blood sampling throughout the study. For studies involving intravenous dosing, catheters were inserted into both left and right cephalic veins such that dosing and blood sampling could be conducted via separate cannulas.

Oral doses of MU were administered as a single soft gelatin capsule (followed by 50 mL of tap water administered via a syringe to the side of the mouth) to lymph-cannulated and nonlymph-cannulated greyhound dogs after an overnight fast (14–16 h). In fasted-state studies, dogs remained fasted throughout the 8-h sample collection period postdosing. In fed-state studies, dogs were fed a weighed quantity of commercial dog food (100–680 g) containing approximately 5% fat 30 to 45 min before dosing. Three-milliliter
blood samples were collected via the cephalic vein cannula immediately before oral dosing and at 15, 30, 45, 60, 75, 90, 105, 120, 180, 210, 240, 360, and 480 min and 24 h post dosing. All the blood samples were collected into individual tubes containing 5 mg of dipotassium EDTA. Plasma was separated by centrifugation (10 min, 1600g) and stored frozen at ~80°C until analysis.

Intravenous doses of MU and M were administered by slow infusion over 5 min via the cephalic vein cannula to nonlymph-cannulated greyhound dogs. The cephalic cannulas were flushed immediately with heparinized saline to ensure the entire dose was administered. Three-milliliter blood samples were taken from the contralateral cephalic vein cannula before dosing (predose), immediately after the dose infusion (time = 0), and at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, 240, 360, and 480 min post dosing.

Blood samples were collected into individual tubes, and the plasma was separated as described above.

Lymph was collected continuously from lymph-cannulated greyhound dogs for 10 h post dose into polypropylene tubes containing 75 mg of disodium EDTA. Lymph collected for each hourly time point was pooled, and the total volume of lymph collected per hour was determined gravimetrically (assuming a specific gravity of 1 g · ml⁻¹). Aliquots of the pooled lymph samples were dispensed into Eppendorf tubes and stored at 4°C until analysis (usually within 24 h). To limit possible dehydration caused by continuous drainage of lymph, a 25-ml bolus of normal saline was administered via the cephalic vein cannula every hour. Water was also available ad libitum throughout the study.

Analysis of MU in lymph and in formulation samples. To prepare lymph samples for analysis, 200 μl of acetonitrile was added to 50 μl of lymph and vortexed for 60 s. Samples were then centrifuged at 1600g for 2 min to pellet lymph proteins. Four milliliters of acetonitrile was then added and vortexed for 2 min to dissolve lymph lipids. After centrifugation (1600g for 5 min), the entire supernatant was transferred to clean tubes, and the solvent was removed by evaporation under nitrogen gas. The resulting sample was then redissolved in 100 μl of acetonitrile for analysis. Formulation samples were diluted at least 100-fold in acetonitrile before analysis by liquid chromatography (LC)/UV.

The HPLC system consisted of a Waters (Milford, MA) 717 Plus Autosampler connected to a Beckman Coulter (Fullerton, CA) Programmable Solvent Module 126 and a Beckman Coulter Programmable Detector Module 166 set at 240 nm. A 25-μl volume of sample was injected onto a Symmetry C₁₈ column (3.9 × 150 mm, i.d. 5 μm; Waters). Mobile phase A consisted of 95% (v/v) water and 5% (v/v) acetonitrile, and mobile phase B consisted of 5% (v/v) water and 95% (v/v) acetonitrile. The initial proportion of mobile phase B was 10%, which was linearly increased to 100% over 10 min and held for 6 min before returning to 10% over the following 2 min. Mobile phase was then held at 10% B for a further 6 min to allow complete washout and re-equilibration before subsequent injection. The total run time was 25 min at a flow rate of 1 ml · min⁻¹. The lower limit of quantitation (LLQ) for MU in lymph and in formulation samples using UV detection was 0.11 μM.

Analysis of M in lymph and analysis of MU and M in plasma. One hundred eighty microliters of acetonitrile was added to a 20-μl aliquot of lymph or plasma, shaken for 10 min, and then centrifuged at 5700 rpm (6120g) for 20 min. To 50 μl of the diluted sample was added 50 μl of dimethyl sulfoxide and 200 μl of acetonitrile containing internal standard (3-benzoyl-2-naphthoic acid, 500 nM), and concentrations of M and MU were quantified by LC/mass spectrometry (MS). The HPLC system was an API 4004 solid-phase extraction (Symbiosis Pharma; Spark, Emmen, The Netherlands) LC/MS (Applied Biosystems/MDS Sciei, Foster City, CA). A 40-μl sample was injected onto a Polaris C₁₈ column (60 × 3.0 mm; Varian, Inc., Palo Alto, CA) maintained at 40°C. MS was performed with positive-ion atmospheric pressure chemical ionization. The needle current was 3 μA, and the nebulizer temperature was 450°C. The MS detector was operated in the multiple reaction monitoring mode. Mobile phase A consisted of water/0.1% formic acid/1.0% isopropyl alcohol, and mobile phase B consisted of methanol/0.1% formic acid/1.0% isopropyl alcohol. A 4-min gradient was used in which the mobile phase composition varied (linearly) from 75% A, 25% B (v/v) to 10% A, 90% B (v/v), followed by 100% B for 1 min, at a flow rate of 0.7 ml · min⁻¹. The LLQ for M in lymph was 6 nM, and for MU and M in plasma samples it was 2.4 and 6 nM, respectively.

Analysis of triglyceride concentration in lymph. Lymph triglyceride concentrations were measured in individual lymph samples using a Roche (Basel, Switzerland) Cobas Mira clinical chemistry analyzer and a commercial enzyme-based colorimetric assay kit (Roche Diagnostics, Mannheim, Germany). Lymph samples were diluted with Milli-Q water before analysis if required.

Data analysis. Maximum plasma concentration (Cmax) and time to reach Cmax (tmax) were determined from inspection of individual plasma concentration versus time plots. The systemic exposure to MU and M after oral and intravenous administration was determined by calculating the area under the plasma concentration versus time curve (AUC) using WinNonlin version 4 (Pharsight, Mountain View, CA) and the linear trapezoidal method. Where the terminal elimination phase was apparent, the area was extrapolated from the last measured plasma concentration to infinity to give AUC∞. Plasma clearance of MU and M after intravenous administration was calculated as the ratio of the intravenous dose to the AUC∞ (i.e., eq. 1),

\[ CL_{i.v.} = D_{i.v.}/AUC_{i.v.}^{\infty} \]  

(1)

The oral bioavailability of MU and M after oral administration of MU was determined by calculating the ratio of dose (D)-normalized AUC∞ after oral administration to the dose-normalized AUC∞ after intravenous administration, i.e. (eq. 2),

\[ BA_{oral} = (AUC_{oral}^{\infty}/D_{oral}) \times (D_{i.v.}/AUC_{i.v.}^{\infty}) \times 100\% \]  

(2)

The apparent systemic conversion of MU to M was determined after intravenous administration of MU by dividing the dose-normalized AUC∞ of M after intravenous administration of MU by the dose-normalized AUC∞ of MU obtained after intravenous administration of M as follows (eq. 3):

\[ \% conversion = \frac{AUC_{M}^{\infty} \text{ after i.v. MU}}{AUC_{MU}^{\infty} \text{ after i.v. M}} \times 100\% \]  

(3)

The proportion of the administered MU dose transported via the lymph (%LT) was calculated by determining the cumulative mass of MU recovered in lymph over the entire lymph collection period and comparing this with the orally administered dose, i.e. (eq. 4),

\[ %LT = \frac{\text{cumulative mass of MU transported in lymph}}{D_{oral}} \times 100\% \]  

(4)

In Vivo Rat Studies. Oral formulations of MU. The formulations used in the in vivo rat studies were based on those previously shown to result in different levels of lymphatic triglyceride transport, and the methods used in the current study are the same as those described previously (Trevaskis et al., 2005). In brief, 1 mg of MU was dissolved in either 4 mg (low lipid load) or 40 mg (high lipid load) of oleic acid or castor oil/Lauroglycol FCC (60:40% w/w), which was then emulsified in a solution of either 0.2% (w/v)/Tween 80 in normal saline, pH 7.4, or in a bile salt (BS) solution comprising 3.6 mM L-α-lysophosphatidylcholine (LPC) and 5 mM sodium taurocholate in phosphate buffer, pH 6.9. A lipid-free formulation was prepared by dissolving 1 mg of MU directly in 0.2% (w/v)/Tween 80. The final volume of all the oral formulations was 5.6 ml. Oral formulations were emulsified by sonication using a probe sonicator (XL-Series; Misonix, Inc.).

Lymphatic transport determinations in rats. The surgical and experimental procedures have been described in detail previously (Edwards et al., 2001; Trevaskis et al., 2005) and were approved by the...
local Institutional Animal Experimentation Ethics Committee. In brief, anesthetized, fasted, male, Sprague-Dawley rats (280–320 g) had a J-shaped polyethylene cannula inserted into the duodenum, 1 cm below the pylorus, and a second cannula inserted into the mesenteric lymph duct. Both cannulas were secured by a drop of instant cyanoacrylate adhesive (Supa Glue; Selleys, Padstow, NSW, Australia). A third cannula was inserted into the trachea to maintain a patent airway throughout the experiment. Animals remained anesthetized throughout the experiment as described previously (Trevaskis et al., 2005), and body temperature was maintained by placing the anesthetized, cannulated animal on a heated pad set at 37°C. Animals were rehydrated by infusing normal saline via the duodenal cannula at a flow rate of 2.8 ml·h⁻¹ for at least 30 min after the completion of the surgery. For administration of MU, the saline infusion was switched to the lipid formulation, which was infused intraduodenally at a rate of 2.8 ml·h⁻¹ for 2 h (5.6 ml total). Normal saline was then reintroduced, and the infusion was continued at 2.8 ml·h⁻¹ for the remainder of the experiment. One group of animals received a predose infusion of a very high-dose lipid formulation [100 mg of oleic acid in BS solution (3.6 mM LPC/5 mM sodium taurocholate in phosphate buffer, pH 6.9)] for 1 h before administration of a high lipid MU formulation (1 mg of MU in 40 mg of oleic acid emulsified in the same BS solution) in an attempt to maximize the availability of lymph lipoprotein precursors in the enterocytes. Lymph was collected continuously over 8 h via the lymph duct cannula into tared polypropylene tubes containing heparin (100 IU) (usually within 24 h). At the conclusion of the experiment, rats were killed humanely by a lethal intraperitoneal dose of 1 ml of sodium pentobarbitone (100 mg·ml⁻¹). Analysis of MU formulations and lymph and analysis of triglyceride content in lymph were conducted using the methods described for the dog studies.

Solubility determinations. The solubility of MU and M in various media was determined at 25°C as MU melts at temperatures greater than 29°C. An excess of either MU or M was weighed into a glass test tube, and the solvent was added. The solvents investigated were water, bile (obtained from beagle dogs) diluted 1:1 (v/v) with phosphate-buffered saline, pH 7.4, soybean oil (a representative long-chain triglyceride), and micellar solutions containing either 20 mM sodium taurodeoxycholate/5 mM sodium taurodeoxycholate/1.25 mM purified egg lecithin or 5 mM soybean oil (a representative long-chain triglyceride), and micellar solutions containing either 20 mM sodium taurodeoxycholate/5 mM sodium taurodeoxycholate/1.25 mM purified egg lecithin in buffer (50 mM Tris maleate, 5 mM CaCl₂, 150 mM NaCl, pH 7.5). Tubes were rotated at 30 rpm for 7 h at 25°C. After incubation, each sample was centrifuged for 20 min at 7200 g to separate undissolved MU or M from the solution. The supernatant was analyzed for measurement of MU and M concentrations.

Analysis of solubility samples. The HPLC system consisted of a Hewlett Packard (Palo Alto, CA) 1100 system equipped with a diode array detector and temperature-controlled column compartment. Mobile phase A was water; mobile phase B was acetonitrile; and mobile phase C consisted of tetrahydrofuran. The initial composition of the gradient was 60% A, 40% B, and 0% C, which changed to 10% A, 90% B, and 0% C over 10 min. This composition was held for 20 min, after which the composition was changed to 0% A, 50% B, and 50% C and held for a further 5 min. The composition then returned to 60% A, 40% B, and 0% C for re-equilibration. The flow rate was 1.0 ml·min⁻¹, and the total run time was 45 min. Twenty-microliter samples were injected onto a Symmetry C₁₈ column (150 × 3.9 mm, 5 μm i.d.; Waters) maintained at 40°C. Detection was achieved at 240 nm.

Results

Pharmacokinetics of MU and M after Intravenous Administration to Greyhound Dogs. Mean plasma concentration versus time profiles for MU and M after intravenous administration to dogs are shown in Fig. 1. The calculated pharmacokinetic parameters for MU and M after intravenous administration to greyhounds are summarized in Table 1. After intravenous infusion of MU, the plasma concentration of MU decreased monoexponentially with an apparent elimination half-life \((t_{1/2})\) of 23.6 min. MU clearance (CL) and volume of distribution \((V_{D})\) after intravenous administration were low (2.2 ml·min⁻¹·kg⁻¹ and 71.8 ml·kg⁻¹, respectively). In contrast, CL and \(V_{D}\) of M after intravenous administration were significantly higher (54.9 ml·min⁻¹·kg⁻¹ and 2530 ml·kg⁻¹, respectively), although the terminal \(t_{1/2}\) was similar (34.4 min) compared with MU. The apparent elimination \(t_{1/2}\) of M was not significantly different after intravenous administration of M and MU (34.4 ± 6.5 min versus 40.2 ± 6.5 min). In this study the systemic conversion of MU to M was estimated according to eq. 3 and was calculated to be approximately 117%. This comparison assumes that the systemic clearance of M is the same after conversion from MU as it is after intravenous administration of M. It also assumes linear pharmacokinetics. The greater than 100% systemic conversion of MU may reflect a deviation from either of these assumptions. Alternatively, it may simply reflect variability in the data acquired across different animals. Nonetheless, approximately complete conversion seems likely.

Pharmacokinetics and Bioavailability of MU and M after Oral Administration of MU to Fed and Fasted Dogs. The mean systemic plasma concentration versus time profiles for MU and M after oral administration of MU to nonlymph-cannulated greyhounds are presented in Fig. 2. Dogs were either fasted or fed a meal containing approximately 34 g of lipid 30 to 45 min before dosing. The calculated pharmacokinetic parameters after oral administration are summarized in Table 2. \(C_{max}\) after oral administration of MU was approximately 40-fold higher in fed animals compared with fasted animals, and the systemic exposure to MU \((AUC^{0-\infty})\) increased 35-fold on administration with food. The absolute bioavailability of MU when administered orally to fed and fasted greyhounds was 2.8 and 0.08%, respectively. Food also increased the systemic exposure to M after oral MU administration approximately 7-fold, from 1.7% oral bio-

![Fig. 1. Mean (±S.E.M., n = 3) plasma concentration profiles of MU (triangles) and M (circles) after intravenous administration of MU (closed symbols) and M (open symbols) to nonlymph-cannulated greyhound dogs.](image-url)
availability in the fasted state to 12.1% after postprandial administration.

**Lymphatic Transport of MU and M in Dogs.** The total mass of MU transported in the lymph of fed and fasted greyhound dogs over 10 h represented 5.8 and 0.11% of the oral dose, respectively (Fig. 3), indicative of a greater than 50-fold increase in lymphatic transport in the presence of food. The plasma concentrations of MU and M in lymph-cannulated greyhounds were less than the LLQ for all the time points in fasted animals, and in fed animals only five individual time points (of 42 total) contained quantifiable levels of M or MU; all the other data were less than the LLQ. Therefore, lymph diversion resulted in negligible systemic exposure to MU and M, suggesting almost complete dependence on lymphatic transport for systemic exposure after oral dosing.

The cumulative percentage of the oral dose of MU transported in the lymph of animals fed varying quantities of food (and hence lipid) increased with total lymph triglyceride transport (Fig. 4). The apparent sigmoidal relationship ($r^2 = 0.9575$) between lymphatic MU and triglyceride transport suggests that a threshold quantity of lipid transport was required to support significant increases in lymphatic drug transport, but that beyond that threshold relatively small changes in lymphatic triglyceride transport resulted in large changes in MU lymphatic transport. At high lipid transport rates, further increases in MU transport were not evident, suggesting that lymphatic lipid transport rates were no longer limiting lymphatic drug transport.

**Lymphatic Transport of MU in Rats.** The lymphatic transport of MU in rats after oral administration in formulations designed to stimulate different rates of triglyceride transport across the enterocyte also increased with increasing lymph triglyceride transport (Figs. 5 and 6). Formulations stimulating low levels of triglyceride transport in lymph (lipid-free or 4 mg of oleic acid) resulted in only low levels of MU transport in lymph; formulations stimulating intermediate levels of triglyceride transport (containing 40 mg of oleic acid or 40 mg of castor oil/Lauroglycol FCC) resulted in intermediate levels of MU transport; and predosing rats with 100 mg of lipid before administration of MU in 40 mg of oleic acid resulted in the greatest extent of MU transport. In the group prefed 100 mg of lipid, lymphatic drug transport was notably delayed compared with the other groups, presumably reflecting the time required to process the very large quantities of coadministered lipid. The maximum rate of triglyceride transport (on a mg · h$^{-1}$ basis) was much lower in rats compared with dogs in both fasted animals and in the presence of lipid or triglyceride-stimulating formulations (Table 3), and this was also reflected in the up to 300-fold difference in total mass of triglyceride transported over the course of the 8- to 10-h study period. Whereas the differences in lymphatic lipid transport largely reflected the differences in lipid mass administered, the maximum rate of MU transport and total quantity of MU transported in lymph per gram of triglyceride were similar in rats and dogs, suggesting that the absolute mass of triglyceride transported into

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MU after Intravenous MU</th>
<th>M after Intravenous MU</th>
<th>M after Intravenous M</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-\infty}$ (nmol · min$^{-1}$ · mmol$^{-1}$)</td>
<td>11,773 ± 1237</td>
<td>773 ± 28</td>
<td>661 ± 185</td>
</tr>
<tr>
<td>CL (ml · min$^{-1}$ · kg$^{-1}$)</td>
<td>2.2 ± 0.3</td>
<td>N.A.</td>
<td>54.9 ± 11.8</td>
</tr>
<tr>
<td>V$_D$ (ml · kg$^{-1}$)</td>
<td>71.8 ± 8.4</td>
<td>N.A.</td>
<td>2530 ± 310</td>
</tr>
<tr>
<td>t$_{1/2}$ (min)</td>
<td>23.6 ± 4.2</td>
<td>40.2 ± 4.1</td>
<td>34.4 ± 6.5</td>
</tr>
</tbody>
</table>

Percentage conversion calculated as the dose-normalized AUC$_{0-\infty}$ of M after intravenous administration of MU divided by the dose-normalized AUC$_{0-\infty}$ of M after intravenous administration of M.

Dose-normalized AUC. Actual doses of MU administered were 0.06 ± 0.004 mg · kg$^{-1}$ (0.14 ± 0.004 μmol · kg$^{-1}$); actual dose of M administered was 0.11 ± 0.002 mg · kg$^{-1}$ (0.39 ± 0.004 μmol · kg$^{-1}$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MU after Intravenous MU</th>
<th>M after Intravenous MU</th>
<th>M after Intravenous M</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Conversion</td>
<td>0.006 ± 0.006</td>
<td>0.004 ± 0.004</td>
<td>N.A.</td>
</tr>
</tbody>
</table>

TABLE 1

Summary of pharmacokinetic parameters for MU and M determined in nonlymph-cannulated greyhound dogs (mean ± S.E.M. for n = 3 dogs) after intravenous administration of MU and M as an intralipid emulsion over 5 min.
As poor intestinal solubility is a potential limitation to the oral bioavailability of MU, the solubility of MU and M was determined in aqueous media, lymph was the most important determinant of MU, and hence M, bioavailability.

**Solubility of MU and M.** As poor intestinal solubility is a potential limitation to the oral bioavailability of MU, the solubility of MU and M was determined in aqueous media, diluted bile, a representative long-chain triglyceride (soybean oil), and micellar solutions representative of both fed and fasted conditions. As expected, the aqueous solubility of MU was low compared with the aqueous solubility of the less lipophilic parent compound (0.42 μg · ml⁻¹ versus 73 μg · ml⁻¹) but much higher in lipid (437 mg · ml⁻¹ versus 10 mg · ml⁻¹). The solubility of both compounds in diluted bile, soybean oil, and simulated intestinal contents was significantly greater than in water alone (Table 4).

### Discussion

The effect of food and, in particular, lipids on the oral bioavailability of poorly water-soluble drugs is well documented. Mechanisms by which increased drug absorption can occur include slowing of gastric emptying, enhancement of gastrointestinal dissolution or solubilization, protection from intestinal degradation, and stimulation of lymphatic drug transport (Charman et al., 1997; Wasan, 2001; Grove et al., 2007; Porter et al., 2007; Dahan et al., 2008). In the current study, the oral bioavailability of MU in fed animals increased 35-fold compared with bioavailability in fasted animals. The bioavailability of M after oral administration of MU also increased substantially postprandially. The postprandial exposures to MU and M were consistent with previous data for the structurally similar TU and testosterone (Tauber et al., 1986; Shackleford et al., 2003), and the increase in exposure compared with fasted state bioavailability was consistent with clinical observations for TU (Bagchus et al., 2003). The data are also consistent with observations for MU in humans (data on file, Schering Plough), which suggest a pronounced increase in MU and M exposure when MU is administered with food.

To explore potential mechanisms underpinning the increase in postprandial exposure, the possible effect of food on intestinal solubilization of MU and M was estimated in vitro. As expected, the aqueous solubility of MU was low but increased dramatically in micellar solutions representative of fasted and fed-state intestinal conditions.

### Table 2

**Summary of pharmacokinetic parameters for MU and M after oral administration of MU to nonlymph-cannulated greyhound dogs in both the fasted and fed states.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fasted</th>
<th>Fed</th>
<th>Mean Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MU</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (nmol · ml⁻¹)</td>
<td>0.02 ± 0.004</td>
<td>0.82 ± 0.08*</td>
<td>41</td>
</tr>
<tr>
<td>AUC_{0-1} (nmol · min · ml⁻¹ · mmol⁻¹)</td>
<td>9.58 ± 2.05</td>
<td>334.38 ± 38.07*</td>
<td>35</td>
</tr>
<tr>
<td>t_{max} (min)</td>
<td>75 (75–90)</td>
<td>240 (210–240)</td>
<td></td>
</tr>
<tr>
<td>Oral bioavailability (%)</td>
<td>0.08</td>
<td>2.8</td>
<td>35</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (nmol · ml⁻¹)</td>
<td>0.01 ± 0.001</td>
<td>0.07 ± 0.01*</td>
<td>7</td>
</tr>
<tr>
<td>AUC_{0-1} (nmol · min · ml⁻¹ · mmol⁻¹)</td>
<td>13.71 ± 0.24</td>
<td>94.57 ± 1.75*</td>
<td>7</td>
</tr>
<tr>
<td>t_{max} (min)</td>
<td>75 (60–105)</td>
<td>90 (75–120)</td>
<td></td>
</tr>
<tr>
<td>Oral bioavailability (%)</td>
<td>1.7</td>
<td>12.1</td>
<td>7</td>
</tr>
</tbody>
</table>

Data represent the mean ± S.E.M. for n = 3 dogs except for t_{max}, which is the median (range) for n = 3 dogs.

* p < 0.01, † p < 0.001.

† Dose-normalized AUC. Actual dose of MU administered was 2.21 mg · kg⁻¹ (4.83 ± 0.1 μmol · kg⁻¹) in fed animals and 1.84 ± 0.12 mg · kg⁻¹ (4.02 ± 0.3 μmol · kg⁻¹) in fasted animals.

* Refers to the bioavailability of M after oral administration of MU and assumes administration of a molar equivalent dose of M.

---

**Fig. 3.** Mean (±S.E.M., n = 3) lymphatic transport of MU (A) and M (B) in lymph duct-cannulated greyhound dogs after oral administration of MU in both the fasted (open symbols) and fed (closed symbols) state. Data represent the total mass of MU and M collected over each time point.
al., 1986); therefore, increases in postprandial absorption alone are unlikely to lead to significant increases in bioavailability without attendant effects on first-pass metabolism. In this regard, MU is highly lipophilic (437 mg L1 solubility in soybean oil and calculated log P 8.73), and for compounds of this type, access to the systemic circulation after oral absorption may occur via the lymphatic system rather than by transport into portal blood (Charman and Stella, 1986; Wasan, 2001; Holm et al., 2002; Hauss, 2007). Lymphatic drug transport is typically increased after postprandial administration because the lipids in food stimulate the synthesis of lymph lipoproteins, which in turn act as carriers for lymphatically transported drugs (Charman and Stella, 1991; Porter and Charman, 2001a; Wasan, 2001; Holm et al., 2002; Hauss, 2007). This result may be particularly important in the case of highly metabolically labile molecules such as M because lymphatic drug transport circumvents presystemic hepatic metabolism and therefore provides an avenue to improved bioavailability.

In the current studies the quantity of MU transported in lymph over a 10-h postdose period was relatively low but increased more than 50-fold in fed versus fasted animals (from 0.11 to 5.8% of the administered dose). It is noteworthy that systemic (blood) levels of MU and M were less than the limit of quantification in lymph-cannulated animals, presumably reflecting conversion of MU to M and subsequent metabolism of M during first pass through the liver. In this regard, a range of hydroxylated metabolites of M have recently been described (Prasad et al., 2009) but were not quantified here. Therefore, intestinal lymphatic transport seems to be essentially the sole mechanism of transport of bioavailable MU and M to the systemic circulation. Given the low blood exposure of M in lymph-cannulated animals and the 10-fold higher concentrations of MU in the lymph compared with M, it is likely that the predominant mechanism of transport of bioavailable MU to the systemic circulation is via lymphatic transport of MU, followed by systemic liberation of M (rather than via lymphatic transport of M or absorption of MU or M via the blood). That the lymphatic transport of MU is significantly more efficient after coadministration with food provides an explanation for the large increase in postprandial bioavailability of M after oral administration of MU.

To explore the quantitative impact of coadministered lipid on the lymphatic transport of MU (and therefore the systemic exposure of M), a series of studies were undertaken to map the changes in lymphatic transport after coadministration with differing quantities of lipid. Low levels of MU lymphatic transport were observed under conditions of basal triglyceride transport. Data are presented as the mean ± SD (n = 3–7). Lipid predose (circles), 40 mg of oleic acid + LPC + BS (crosses), 40 mg of oleic acid in Tween (inverted triangles), 40 mg of castor oil/Lauroglycol FCC in Tween (closed squares), 2 mg of castor oil/Lauroglycol FCC + LPC + BS (diamonds), 4 mg of oleic acid + LPC + BS (upright triangles), and lipid-free formulation (open squares). Refer to text for full formulation details.

Fig. 4. Percentage of the lymphatically transported dose of MU recovered in the lymph of cannulated greyhound dogs after oral administration with different lipid loads. A, as a function of time: 34 g of lipid, mean ± S.E.M., n = 3 (circles); 15 g of lipid, n = 1 (upright triangles); 10 g of lipid, n = 1 (diamonds); 7.5 g of lipid, n = 1 (crosses); 5 g of lipid, n = 1 (inverted triangles); fasted, mean ± S.E.M., n = 3 (squares). B, as a function of total triglyceride (TG) transport. Data are presented as the percentage of the dose recovered after coadministration with different lipid loads relative to the percentage of MU dose transported in lymph after administration of 34 g of lipid (closed circles). Previously reported data for an unrelated highly lipophilic antimalarial (halofantrine) is plotted for comparison (open circles) (Khoo et al., 2003). Three-parameter sigmoidal regression conducted using SigmaPlot, version 10.0 (Systat Software, Inc., San Jose, CA), r² = 0.9575.

Fig. 5. Percentage of the lymphatically transported dose of MU recovered in the lymph of duct-cannulated rats after oral administration in formulations designed to stimulate varying rates of triglyceride transport. Data are presented as the mean ± SD (n = 3–7). Lipid predose (circles), 40 mg of oleic acid + LPC + BS (crosses), 40 mg of oleic acid in Tween (inverted triangles), 40 mg of castor oil/Lauroglycol FCC in Tween (closed squares), 2 mg of castor oil/Lauroglycol FCC + LPC + BS (diamonds), 4 mg of oleic acid + LPC + BS (upright triangles), and lipid-free formulation (open squares). Refer to text for full formulation details.
lipid loads (Table 3). It is interesting to note that when data obtained in the same model for the structurally unrelated (but lymphatically transported) antimalarial halofantrine (Khoo et al., 2003) are compared with the current MU data, the relationship between lymphatic lipid and drug transport is similar (Fig. 4B). In the case of halofantrine, however, the correlation is even more pronounced, and significant lymphatic drug transport was evident at much lower lymph triglyceride levels than that observed for MU, and much higher drug/triglyceride levels were apparent in the lymph. The apparently greater mass of triglyceride required to stimulate lymphatic transport of MU compared with halofantrine is unlikely to reflect differences in lipophilicity because MU is at least as lipophilic as halofantrine when assessed by Log P (8.73 versus 8.5) (Porter et al., 1996) and solubility in long-chain triglycerides (437 versus 47.3 mg·ml⁻¹) (Kaukonen et al., 2004). However, maximum concentrations of MU per gram of lymphatically transported lymph triglyceride were much lower than that of halofantrine (<1% versus ~25% of the equilibrium solubility of drug in triglyceride) (Khoo et al., 2003), suggesting that factors other than solubility in lymph triglyceride were limiting MU lymph transport. In this regard, an important differential between halofantrine and MU is the potentially lower metabolic stability of MU in the enterocyte. In the current studies, the efficiency of enterocyte-based conversion of MU to M was evaluated in a previously described isolated perfused rat intestine model (Johnson et al., 2003). After perfusion of an MU emulsion through an isolated section of jejunum in anesthetized rats, the concentrations of MU in blood draining the perfused intestinal segment were below the limits of quantification at all the time points, whereas appearance of M was clearly evident (data not shown). This finding confirmed that a significant proportion of the presystemic conversion of MU to M occurred in the enterocyte, consistent with previous reports for TU (Coert et al., 1975; Horst et al., 1976). Unpublished investigations have also shown that plasma esterases play a negligible role in the hydrolysis of MU and that hydrolysis by hepatic esterases is considerably more avid (data on file, Schering Plough). In the latter study, conversion by enterocyte-based enzymes was not studied, but collectively these data suggest that after oral administration facile conversion of MU to M will occur on first pass both in the enterocyte and in the liver. Conversely, plasma esterases are unlikely to play a significant role in MU to M conversion. Halofantrine is also converted to a less lipophilic and poorly lymphatically transported metabolite desmethylhalofantrine (Khoo, 2002) within the enterocyte (Porter and Charman, 2001b). However, halofantrine is not a high extraction efficiency drug; therefore, the extent of enterocyte-based conversion of halofantrine to desbutylhalofantrine is considerably lower than that of MU to M.

Previous studies have suggested that increasing the mass of lipid within the enterocyte may reduce drug exposure to enterocyte-based metabolic enzymes (Van Veld et al., 1987; Trensavisk et al., 2006) and that inhibition of enterocyte-based cytochrome P450 metabolism and intestinal P-glycoprotein efflux may significantly enhance the extent of lymphatic transport of metabolically labile drugs (Griffin and O’Driscoll, 2008). Therefore, in light of the significant extent of enterocyte-based conversion of MU to M, the differences in the lipid dependence of lymphatic transport of MU and halo-
In conclusion, the oral bioavailability of M was low after oral coadministration of MU or halofantrine with different lipid loads.

Solubility of MU and M

<table>
<thead>
<tr>
<th>Solubility</th>
<th>MU</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg · ml⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>0.0004</td>
<td>0.073</td>
</tr>
<tr>
<td>Bile</td>
<td>2.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>437</td>
<td>10.0</td>
</tr>
<tr>
<td>Fasted-state micelles²⁸</td>
<td>0.24</td>
<td>0.13</td>
</tr>
<tr>
<td>Fed-state micelles²⁸</td>
<td>1.2</td>
<td>0.31</td>
</tr>
</tbody>
</table>

²⁸ Bile obtained from beagle dogs diluted 1:1 (v/v) in phosphate-buffered saline, pH 7.4.

²⁹ Five millimolar sodium taurodeoxycholate/1.25 mM purified egg lecithin in buffer (50 mM Tris maleate, 5 mM CaCl₂, 150 mM NaCl, pH 7.5).

²³ Twenty millimolar sodium taurodeoxycholate/0.5 mM purified egg lecithin in buffer (50 mM Tris maleate, 5 mM CaCl₂, 150 mM NaCl, pH 7.5).

Halofantrine* ME/LC (fasted) 850 3.4 12.29 4.2
ME/MC (fasted) 178 0.9 5.14 2.8
PEG melt (fasted) N.M. 0.5 4.81 2.6
PEG melt (34 g of lipid) N.M. 32.6 6.21 1.7

N.M., not measured.

* Data reproduced from Khoo et al. (2003). ME/LC, long-chain triglyceride microemulsion; LC/MC, medium-chain triglyceride microemulsion; PEG melt, lipid-free amorphous PEG 600 solid dispersion.

For abbreviations refer to Fig. 6.

TABLE 3
Comparison of mean triglyceride (TG) transport and drug transport rates in lymph of dogs and rats after oral coadministration of MU or halofantrine with different lipid loads

<table>
<thead>
<tr>
<th>Species/Drug</th>
<th>Formulation or Lipid Load</th>
<th>Maximum Rate of TG Transport in Lymph</th>
<th>Total TG Transported in Lymph over 8/10 h</th>
<th>Maximum Rate of Drug Transport in Lymph per Gram TG</th>
<th>Total Drug Transported in Lymph per Gram TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog MU</td>
<td>0 g of lipid (fasted)</td>
<td>461 mg/h g</td>
<td>1.4</td>
<td>0.27 mg drug/g TG</td>
<td>0.07 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>5 g of lipid</td>
<td>745 mg/h g</td>
<td>4.1</td>
<td>0.94 mg drug/g TG</td>
<td>0.19 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>7.5 g of lipid</td>
<td>1374 mg/h g</td>
<td>5.2</td>
<td>1.12 mg drug/g TG</td>
<td>0.45 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>10 g of lipid</td>
<td>2791 mg/h g</td>
<td>7.0</td>
<td>1.51 mg drug/g TG</td>
<td>0.62 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>15 g of lipid</td>
<td>2101 mg/h g</td>
<td>11.7</td>
<td>0.93 mg drug/g TG</td>
<td>0.25 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>34 g of lipid</td>
<td>5015 mg/h g</td>
<td>20.45</td>
<td>0.77 mg drug/g TG</td>
<td>0.23 mg drug/g TG</td>
</tr>
<tr>
<td>Rat** MU</td>
<td>Lipid-free</td>
<td>2.88 mg/h g</td>
<td>0.017</td>
<td>0.55 mg drug/g TG</td>
<td>0.16 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>4 mg of OA + LPC + BS</td>
<td>3.18 mg/h g</td>
<td>0.017</td>
<td>0.52 mg drug/g TG</td>
<td>0.11 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>4 mg of CO/PGL + LPC + BS</td>
<td>3.41 mg/h g</td>
<td>0.020</td>
<td>1.25 mg drug/g TG</td>
<td>0.15 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>40 mg of CO/PGL in Tween</td>
<td>5.72 mg/h g</td>
<td>0.028</td>
<td>1.03 mg drug/g TG</td>
<td>0.41 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>40 mg of OA + LPC + BS</td>
<td>9.94 mg/h g</td>
<td>0.034</td>
<td>0.60 mg drug/g TG</td>
<td>0.52 mg drug/g TG</td>
</tr>
<tr>
<td></td>
<td>100 mg of lipid predose</td>
<td>16.97 mg/h g</td>
<td>0.072</td>
<td>0.56 mg drug/g TG</td>
<td>0.32 mg drug/g TG</td>
</tr>
</tbody>
</table>

μM, not measured.

TABLE 4
Solubility of MU and M

<table>
<thead>
<tr>
<th>Solubility</th>
<th>MU</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg · ml⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>0.0004</td>
<td>0.073</td>
</tr>
<tr>
<td>Bile</td>
<td>2.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>437</td>
<td>10.0</td>
</tr>
<tr>
<td>Fasted-state micelles²⁸</td>
<td>0.24</td>
<td>0.13</td>
</tr>
<tr>
<td>Fed-state micelles²⁸</td>
<td>1.2</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Fantrine may reflect the requirement for a larger intracellular lipid pool to protect the more metabolically labile MU from conversion to M before substantial lymphatic transport can occur.

To confirm that the lipid dependence of MU lymphatic transport was not species-specific, a subsequent series of experiments was conducted in rats. Similarly to the data obtained in dogs, a strong relationship between triglyceride transport and drug transport was evident. Despite differences in the rate and extent of total triglyceride transport, the ratio of MU transported in lymph to total lymph triglyceride was broadly similar (0.16–0.52) to that observed in dogs (0.07–0.62) and independent of the formulation used, further supporting the hypothesis that it is triglyceride transport that supports lymphatic transport of MU rather than the formulation per se.

In conclusion, the oral bioavailability of M was low after oral administration of MU under fasted conditions but increased dramatically after coadministration with food. Significant increases in lymphatic transport of MU were also shown postprandially, and data obtained in lymph-cannulated dogs suggest that the increase in M bioavailability was derived almost entirely from lymphatic transport of MU. Subsequent studies further elucidated, in both rats and dogs, that lymphatic transport of MU was highly dependent on the mass of triglyceride transported in the lymph, especially in the period immediately after dosing. The high lymphatic lipid flux required to stimulate substantial MU transport may reflect the need for protection from enterocyte-based hydrolysis because conversion of MU to the less lipophilic M is facile and expected to limit lymphatic transport. The latter suggestion is consistent with recent studies that have shown that inhibition of enterocyte-based efflux and metabolism leads to an increase in lymphatic transport of the metabolically labile protease inhibitor saquinavir (Griffin and O’Driscoll, 2008).

Acknowledgments

We thank Janine Zwerink for analytical support and Dr. David Shackelford for pharmacokinetic advice.

References


Coet A, Geelen J, de Visser J, and van der Vies J (1975) The pharmacology and...


Lipid Dependency of MU Lymph Transport and M Bioavailability 709


Address correspondence to: Christopher J. H. Porter, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), VIC 3052, Australia. E-mail: chris.porter@pharm.monash.edu.au