Effect of Bile on Absorption of Mepitiostane by the Lymphatic System in Rats

TERUHISA ICHIHASHI, HARUKI KINOSHITA, YASUSHI TAKAGISHI AND HIDEO YAMADA*

*Shionogi Research Laboratories, Shionogi & Co. Ltd, Fukushima-Ku, Osaka 553, Japan, and
School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan

Abstract—The effects of bile and site of gastrointestinal absorption on the lymphatic absorption of the highly lipophilic drug, mepitiostane were examined using thoracic duct-cannulated rats. The lymphatic absorption from the small intestine was very small in the absence of bile compared with that when bile was present. The lymphatic absorption was greatest when drug was administered to the upper small intestine with bile, was smaller for the lower regions of the small intestine, and was negligible for the stomach and the large intestine. A correlation was observed between the extent of lymphatic absorption and the secretion of chylomicron and very low density lipoproteins after administration to various regions with or without bile. The portal absorption data of mepitiostane confirmed that site specificity occurs in the partition of drug between blood and lymph.

The intestinal absorption of nutrients and drugs is dependent on the site of absorption in the gastrointestinal tract and by the presence of bile. For example, bile acids are known to play an important role in the intestinal absorption of fats (Holt 1972; Ockner & Isselbacher 1974), cholesterol (Siperstein et al 1952; Holt 1972) and lipid-soluble vitamins (Quick et al 1954; Olson 1964). The absorption of water-insoluble drugs is enhanced by the presence of bile (Steinetz et al 1965; Palma et al 1986). Riboflavin, fat, monosaccharides and lipid-soluble vitamins are well absorbed in the proximal small intestine, while the optimal absorption site of bile acids and vitamin B_{12} is the ileum (Booth 1967; Levy 1966). However, little information is available about the effect of bile and absorption site on the lymphatic transfer of drugs.

We previously found (Ichihashi et al 1991a, b), that the anti-mammary tumour agent mepitiostane is absorbed almost exclusively by the lymphatic system in rats. The present study was designed to investigate the effects of bile and site of gastrointestinal absorption on the lymphatic absorption of mepitiostane as a model compound absorbed via the lymphatic route.

Materials and Methods

Materials

[4-^{14}C]Mepitiostane (10·6 μCi mg^{-1}) was synthesized at Shionogi Research Laboratories. Its radiochemical purity was confirmed by TLC (Merck Silica Gel 60, petroleum ether-ethyl ether (10:1)) to be >98%. Other chemicals and reagents were of analytical or reagent grade. The oily solution was prepared by dissolving [^{14}C]mepitiostane in sesame oil (10–30 mg mL^{-1}).

Animals

Sprague-Dawley rats (female: 11–13 weeks, male: 8 weeks) were purchased from CLEA Japan, Inc., Tokyo, and maintained on commercial chow (CA1 pellets, CLEA Japan,

Correspondence: T. Ichihashi, Shionogi Research Laboratories, Shionogi & Co. Ltd, 5-12-4 Sagisu, Fukushima-ku, Osaka 553, Japan.

Inc.) with free access to water until surgery. In the case of drug administration to the stomach and large intestine, the animals were starved overnight before surgery. All rats were anaesthetized with ethyl urethane (1·4 g kg^{-1}, s.c.) and following abdominal incision, the thoracic duct was cannulated by a modification of the method of Bollman et al (1948), using polyethylene tubing (PE50, Becton Dickinson and Co., Parsippany, NJ, USA). Two cannulae (PE50) were introduced into the common bile duct, one for collecting bile and the other for providing bile from another rat. Both ends of the small intestine (from the pylorus to the ileocaecal valve) were ligated and 1% [^{14}C]mepitiostane in sesame oil (50 mg) dispersed in 1·5 mL fresh rat bile (containing pancreatic juice) was instilled into the lumen. After drug administration, the rats were secured on a warmed plate maintained at 38°C. Lymph and bile were collected in a test tube via the cannulae for 6 h after dosing. Bile (containing pancreatic juice) collected from other rats was instilled into the lumen at the rate of 0·6 mL h^{-1} from 1 h after dosing. Under the bile-deficient condition, 1% [^{14}C]mepitiostane in sesame oil (50 mg) or this solution dispersed in 1·5 mL of 0·9% NaCl (saline) containing 0·2% polysorbate 80 was administered to the small intestine 3 h after cannulation of the bile duct.

To compare the regional capacities for lymphatic absorption of mepitiostane, the gastrointestinal tract of rats was divided into the following six loops by ligature: the stomach, the 8 cm length from the pylorus to the Treitz (upper intestine I), the 20 cm length from the Treitz (upper intestine II), the 20 cm length of the middle (middle intestine), the 20 cm length of the terminal ileum (lower intestine) and large intestine. Under ethyl urethane anaesthesia, [^{14}C]mepitiostane in sesame oil (1%) was administered into the stomach loop at a dose of 1·6 mg kg^{-1}. For the other sites, [^{14}C]mepitiostane in sesame oil (1%) was dispersed in 30 vol of bile (containing pancreatic juice) and administered into each loop at a dose of 1·6 mg kg^{-1}, except for the upper intestine I region (0·6 mg kg^{-1}).

For experiments to estimate the amount of unchanged mepitiostane transferred into the portal system, the rat was placed under ethyl urethane anaesthesia and the thoracic

Table 1. Effects of sex and dose on absorption of mepitiostane (MP) by the lymphatic system and on its distribution between chylomicron + VLDL and infranatant fractions in lymph.

Sex	Dose (mg kg^{-1})	% of dose absorbed (6 h)	% of absorbed dose in lymph	% of lymph MP in chylomicron + VLDL	Lymph flow (g h^{-1})
Female	0·16	76·7 ± 5·1	51·5 ± 5·5	95·1 ± 1·6	0·57 ± 0·09
Female	1·8	74·8 ± 10·9	55·0 ± 4·2	94·8 ± 1·3	0·49 ± 0·13
Female	5·3	71·0 ± 3·0	54·1 ± 1·2	94·9 ± 0·6	0·49 ± 0·06
Male	2·0	76·4 ± 3·8	54·8 ± 2·3	94·9 ± 0·4	0·97 ± 0·17

A sesame oil solution of 0·1%, 1% or 3% [14C]mepitiostane (50 mg) dispersed in fresh rat bile (1·5 mL) was administered into the small intestine of rats, and the thoracic duct lymph was collected for 6 h after dosing. Each value represents the mean ± s.d. of at least 3 rats.

duct and the tail vein were cannulated with heparin-filled polyethylene tubing (PE50). A loop of the test site of intestine (upper intestine I: about 2 cm, others: about 5 cm) was made by ligation at both ends. After injection of 0·7 mL of dilute heparin (2000 units mL^{-1}) via the tail vein, a third cannula filled with dilute heparin was introduced into the mesenteric vein governing the test segments. Immediately, [14C]mepitiostane in sesame oil (3%) dispersed in 30 vol of bile (0·2–0·5 mL) was instilled into this loop. The rats were placed on a warmed plate and the mesenteric venous blood and lymph were collected in the test tube for a 2 h period after dosing, under blood transfusion via the tail vein.

Lipoprotein separation
The chylomicron and very low density lipoprotein fraction (Ch + VLDL fraction) of lymph was separated from the infranatant phase by ultracentrifugation (144000 g for 16 h at 4°C) using a Beckman (California) L2-65B ultracentrifuge according to the method of Hatch & Lees (1968).

Analytical procedures
Measurement of radioactivity. Samples of lymph, bile, urine and other lipids were added to 10 mL of Monophase 40 (Packard Instrument Co. Inc., Illinois, USA) and radioactivity was measured with a liquid scintillation counter (Aloka Co., Tokyo, Japan, Model LSC-673). The small intestine was homogenized after adding water, and the carcass was heated under reflux for 2 h in 150 mL of 6 M HCl. A fraction of each sample was combusted using a sample oxidizer (Packard Tri-carb, Model 306) and the radioactivity was determined by liquid scintillation counting.

Measurement of mepitiostane. Lymph (0·2 mL) was extracted twice with 5 mL of ethyl ether containing 0·1% triethyla-

mine. Blood (2 mL) was diluted with 4 mL of water and extracted twice with 6 mL of ethyl ether containing 0·1% triethylamine after the addition of 4 mL of acetone. All extracts were evaporated, and analysed by TLC (Merck Silica Gel 60 plate, petroleum ether (boiling range 30–60°C)-diethyl ether (10:1)) as described previously (Ichihashi et al 1991a).

Measurement of triglyceride. Triglyceride was measured by a modification of the method of Sardesai & Manning (1968) using a Triglyceride-Test kit (Wako Chemicals, Osaka, Japan).

Results and Discussion

Sex and dose effects
Table 1 shows the effects of sex and dose on the absorption of mepitiostane by the lymphatic system and on the distribution within the lymph components. When [14C]mepitiostane was administered into the small intestine of female rats in three dose levels, 71–77% of the dose was absorbed at 6 h and 52–55% of the absorbed amount was recovered as unchanged drug in the 6 h lymph. These percentages were not significantly different among the three dose levels. For all doses, about 95% of lymph mepitiostane was localized in the Ch + VLDL fraction. The percentage of lymph mepitiostane carried by the chylomicron and VLDL remained approximately constant at the three dose levels. When [14C]mepitiostane was administered to male rats, about 55% of the absorbed amount was recovered as unchanged drug in lymph, and most of this was localized in the Ch + VLDL fraction. Thus, no sex differences were observed in the lymphatic absorption behaviour of mepitiostane. In subsequent experiments, female rats only were used.

Table 2. Effect of bile on the appearance of lymph mepitiostane following administration of [14C]mepitiostane.

Treatment	% of dose absorbed (6 h)	% of absorbed dose in lymph	Lymph flow (g h^{-1})
With bile[a]	74·8 ± 10·9	55·0 ± 4·2	0·49 ± 0·13
Bile-deficient[b]	3·2 ± 1·7	4·7 ± 3·8	0·37 ± 0·06
Bile-deficient[c] (with polysorbate-80)	14·7 ± 0·5	10·5 ± 4·1	0·32 ± 0·04

[a][14C]Mepitiostane in sesame oil (1%) was dispersed in 30 vol of fresh rat bile. [b][14C]Mepitiostane in sesame oil (1%) alone. [c][14C]Mepitiostane in sesame oil (1%) was dispersed in 30 vol of saline containing 0·2% polysorbate 80. Each solution of [14C]mepitiostane was administered into the small intestine of bile fistula rats at a dose of 1·8 mg kg^{-1} and thoracic duct lymph was collected for 6 h after dosing. Each value represents the mean ± s.d. of at least 3 rats.

Table 3. Regional differences of the appearance of lymph mepitiostane following administration of [¹⁴C]mepitiostane.

Region	% of dose absorbed (6 h)	% of absorbed dose in lymph	Lymph flow $(g\ h^{-1})$
Stomach	5·4±1·0	0·0±0·0	0·29±0·08
Small intestine			
Upper I	62·1±1·8	55·9±11·8	0·40±0·18
Upper II	65·7±14·3	57·5±10·1	0·52±0·10
Middle	39·7±8·6	27·8±5·6	0·35±0·07
Lower	15·7±4·9	5·8±6·5	0·45±0·20
Large intestine	12·9±2·1	0·0±0·0	0·22±0·07

[¹⁴C]Mepitiostane in sesame oil (1%) was administered into the stomach of rats at a dose of 1·6 mg kg⁻¹. For other sites, [¹⁴C]mepitiostane in sesame oil (1%) was dispersed in 30 vol of bile and administered at a dose of 1·6 mg kg⁻¹, except for the upper small intestine I region (0·6 mg kg⁻¹). Thoracic duct lymph was collected for 6 h after dosing. Each value represents the mean±s.d. of 3 rats.

Bile effects

Table 2 shows the effect of bile on the absorption of mepitiostane by the lymphatic system. When [¹⁴C]mepitiostane in sesame oil dispersed in bile was administered into the small intestine of bile fistula rats, 74·8% of the dose was absorbed and 55·0% of the absorbed amount was recovered as unchanged drug in the 6 h lymph. In contrast, after administration of [¹⁴C]mepitiostane in sesame oil without bile, the absorption was very slow and the percentage of mepitiostane transferred into the lymph based on the absorbed amount was only about one-tenth of that of the bile-administered rats. When the [¹⁴C]mepitiostane sesame oil solution had been dispersed in saline solution containing 0·2% polysorbate 80, the percentage of absorbed radioactivity increased; however, the extent of lymphatic absorption of mepitiostane was still small. The extents of lymphatic absorption of p,p'-DDT (Sieber et al 1974), Sudan blue (Noguchi et al 1975) and vitamin A (Noguchi et al 1975) decrease in the absence of bile. Similarly, bile was found to be essential for the lymphatic transfer of mepitiostane.

Regional differences

Table 3 shows the regional differences of the absorption of mepitiostane by the lymphatic system. The highest percentage of drug appearing in the 6 h lymph based on the absorbed amount was obtained after administration into the upper small intestine I and the upper small intestine II regions. This percentage decreased in the order of the middle and the lower

region of the small intestine, and no drug was transferred into the lymph from the stomach and the large intestine. These findings agree with the report of Noguchi et al (1977) that the lymphatic transfer of Sudan blue occurred only in duodenal and jejunal regions.

Following the administration of [¹⁴C]mepitiostane into various regions of the intestine of thoracic duct-cannulated rats, 6–16% of the radioactivity administered was also recovered in bile, and thus some of the radioactivity had been absorbed via the portal pathway. The portal absorption of mepitiostane from various regions of the intestine was next examined to clarify the proportions of absorbed drug transferred by the portal and lymphatic routes. Table 4 shows the cumulative amount of radioactivity and unchanged drug in the blood collected from the mesenteric vein governing the test loop following the administration of [¹⁴C]mepitiostane. Within various regions, only 11–18% of the blood radioactivity was due to unchanged drug. The percentage of mepitiostane absorbed into the blood was calculated by multiplying this value (% mepitiostane of the blood radioactivity) by the percentage of radioactivity transferred into the blood, obtained from the results (Table 3). Fig. 1 shows the proportions of absorbed drug transferred by the portal and lymphatic routes in various regions. In the upper small intestine, 87% of mepitiostane was partitioned into the lymphatics and 13% to blood capillaries following passage through the mucosal cell. The proportion of drug partitioned into the lymph was less in the lower region (25%
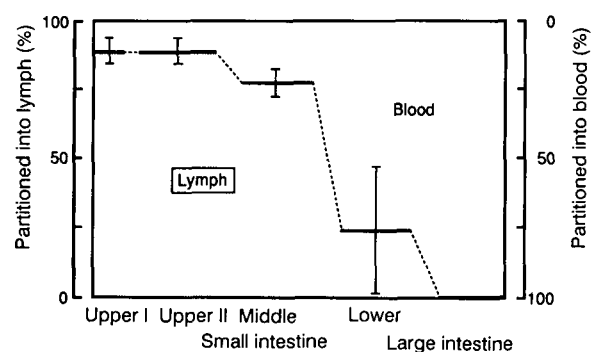

FIG. 1. Proportions of absorbed mepitiostane transferred by lymph and blood over 6 h. [¹⁴C]Mepitiostane sesame oil solution (1%) was dispersed in 30 vol of bile and administered at a dose of 1·6 mg kg⁻¹, except for the upper small intestine I region (0·6 mg kg⁻¹). Each value represents the mean±s.d. of 3 rats.

Table 4. Unchanged mepitiostane in mesenteric blood at 2 h following administration of [¹⁴C]mepitiostane.

Administration site	n	Blood volume (g/2 h)	Radioactivity[a] (μg/2 h)	Mepitiostane (μg/2 h)	Mepitiostane (%)
Small intestine					
Upper I	1	26·2	6·08	0·94	15·4
Upper II	3	25·1±7·2[b]	4·01±0·89[b]	0·71±0·08[b]	18·0±2·7[b]
Middle	1	35·2	6·72	0·74	11·0
Lower	3	18·3±7·0[b]	1·14±1·01[b]	0·14±0·09[b]	14·0±3·3[b]
Large intestine	2	18·2[c]	0·99[c]	0·13[c]	13·2[c]

[a] Mepitiostane equivalent. [b] Mean±s.d. [c] Mean. [¹⁴C]Mepitiostane in sesame oil (3%) was dispersed in 30 vol of bile and administered into various regions of the rat intestine at a dose of 1 mg kg⁻¹.
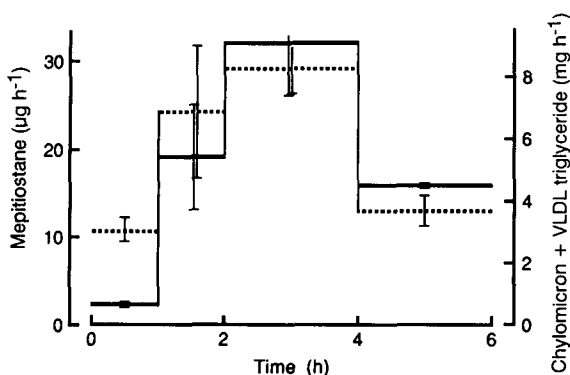
FIG. 2. Transfer rates of mepitiostane (——) and triglyceride (- - -) into thoracic duct lymph following intrajejunal administration of [^{14}C]mepitiostane in sesame oil. Dose of [^{14}C]mepitiostane was 1·8 mg kg^{-1}. Each value represents the mean±s.d. of 3 rats.

into the lymph, 75% into the blood). In the large intestine, all of the drug was partitioned into the blood. Thus, site specificity was observed in the partitioning of mepitiostane between the blood and the lymph.

Relationship between lymphatic transfer of mepitiostane and chylomicron secretion

Fig. 2 shows the time courses of transfer rates of mepitiostane and triglyceride as an indicator of chylomicron and VLDL (Ch+VLDL) into the lymph following intrajejunal administration of [^{14}C]mepitiostane in sesame oil. The transfer rates of mepitiostane and triglyceride into the lymph reached a peak value at 2–4 h after dosing and indicated a similar change. These results, together with the fact that most of mepitiostane in lymph is localized in the Ch+VLDL fraction (Table 1), suggest that Ch+VLDL plays a role as carrier in the lymphatic transfer of mepitiostane.

The triglyceride in the Ch+VLDL fraction of lymph was next measured following the administration of [^{14}C]mepitiostane in different formulations into various regions of the intestine.

Fig. 3 shows the relationship between the percentage of mepitiostane based on the total absorbed amount (from

Table 2) and the amount of Ch+VLDL triglyceride transferred into the lymph by 6 h following the administration of [^{14}C]mepitiostane in sesame oil into the small intestine with or without bile. When bile was present, 55% of the total absorbed amount was transferred as mepitiostane into the lymph and 35 mg of triglyceride was recovered in this lymph. In contrast, in the absence of bile, the amount of Ch+VLDL triglyceride in lymph decreased significantly and then, the extent of lymphatic absorption of mepitiostane was very small. In the process of fat absorption, bile acids play an important role, not only in lipolysis (Borgström 1954; Borgström et al 1957) and micellar solubilization (Hofmann & Borgström 1962; Hofmann & Small 1967), but also in the intramucosal metabolism (Borgström 1953; Dawson & Isselbacher 1960). Gallagher et al (1965) showed that when oleic acid and triolein were administered to bile-deficient rats, the extent of lymphatic transfer of fat decreased significantly compared with normal rats. Also, Ockner et al (1969) suggested that bile salts may enhance the transport of mucosal chylomicron lipids into lymph. The lower lymphatic transfer of mepitiostane in the absence of bile, as shown in Table 2, appears to be due to a decrease in the secretion rate of chylomicron and VLDL. Noguchi et al (1975) have reported that the decrease of lymphatic transfer of lipid-soluble compounds in the absence of bile was restored by the co-administration of both sodium taurocholate and egg phosphatidylcholine.

Fig. 4 shows the relationship between the percentage of mepitiostane transferred into the lymph based on the total absorbed amount (from Table 3) and the amount of triglyceride transferred into the lymph 6 h after administration of [^{14}C]mepitiostane in sesame oil into various regions. The triglyceride increment was calculated by subtracting the triglyceride in 6 h lymph after administration of saline (large intestine, 5·6±0·8 mg; other, 6·8±0·1 mg) from that when [^{14}C]mepitiostane in sesame oil had been administered into various regions. The triglyceride increment was very large in the upper regions of the small intestine and became smaller at the lower region. The increment was negligible in the large intestine. This agreed with the reports of Clark et al (1973) and Sabesin et al (1975) that the intracellular triglyceride
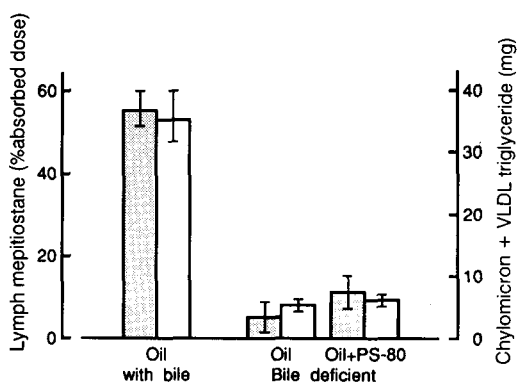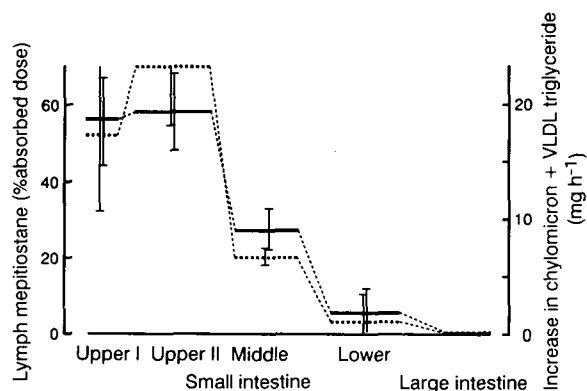

FIG. 3. Relationship between mepitiostane (shaded bar) and chylomicron+VLDL triglyceride (open bar) transferred into lymph 6 h after administration of [^{14}C]mepitiostane into the small intestine. Dose of [^{14}C]mepitiostane was 1·8 mg kg^{-1}. Each value represents the mean±s.d. of 3 rats.

FIG. 4. Relationship between mepitiostane (——) and increment of chylomicron+VLDL triglyceride (- - -) in lymph 6 h after administration of [^{14}C]mepitiostane in sesame oil into various intestinal regions. Dose of [^{14}C]mepitiostane was 1·6 mg kg^{-1}, except for the upper small intestine I region (0·6 mg kg^{-1}). Each value represents the mean±s.d. of 3 rats.

accumulation and the delayed chylomicron secretion were observed in the distal, but not in the proximal, rat intestine. As can be seen in Fig. 4, the highest percentage of mepitiostane transferred into the lymph, based on the absorbed amount, was also observed in the upper small intestine and its percentage was smaller in the lower regions. Thus, a correlation was observed between the lymphatic transfer of mepitiostane and the secretion of chylomicron. Mepitiostane seems to be distributed in the chylomicron and VLDL and transferred into the lymph in the upper small intestine, but since the lower region of the small intestine and large intestine do not secrete chylomicron, mepitiostane is transferred into the blood rather than the lymph.

Yoshikawa et al (1981) have shown that when a bleomycin dextran sulphate complex together with mixed micelles was administered intraluminally, the concentration of bleomycin in the lymph was much higher than in the plasma, and this lymphotropic selectivity was more effective in the large intestine than in the small intestine. In this case, the bleomycin–dextran sulphate complex may be transferred into the lymph even in the large intestine where there is no chylomicron secretion, because the complex itself is a macromolecule and will be excluded from the blood capillaries. For the lymphatic transfer of small–molecular weight compounds, such as mepitiostane, Sudan blue (Noguchi et al 1977) and menaquinone-4 (Ichihashi et al 1992), carriers for lymphatic transfer, such as chylomicron and VLDL are needed, and the upper small intestine, where chylomicron and VLDL are secreted is the most favourable region for lymphatic absorption.

Acknowledgement

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