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Effect of medium-chain glycerides on the intestinal absorption and the hepatobiliary transport of Phenol red

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Summary

The effects of medium-chain glyceride (MGK) on the intestinal absorption and the hepatobiliary transport of Phenol red (PR) were investigated in rats. The in situ recirculation experiment using the small intestine showed that disappearance of PR from the recirculated MGK emulsion at a lipid content of 4% was over 5 times greater than that from the buffer solution, although the effect diminished with the increase of the lipid content. On the contrary, in the everted sac experiments, mucosal to serosal transport of PR from MGK emulsion was reduced to about one half of the control, and the pretreatment with PR-free MGK emulsion could not enhance PR disappearance from the buffer solution recirculated successively. The effect of a polyoxyethylene derivative of castor oil (HCO-100) employed for emulsion preparation on the transport of PR was investigated by the everted sac experiments. The amount of PR transported was decreased with the increase of HCO-100 in the range of 0.1–2.0%. These results may suggest that other factors are related with the promoting effect except for the membrane permeability. When the absorption of MGK components was examined by in situ and in vitro studies, the disappearance of MGK components in the former was nearly twice of that in the latter. The inhibiting effect of MGK on the biliary excretion of PR was observed in the in situ recirculation study with MGK emulsion containing PR. The biliary excretion percent of PR was also significantly reduced by injecting the components of MGK into the mesenteric vein.

Introduction

Recently, many attempts to enhance the absorption of poorly absorbed drugs from the small intestine, rectum (Muranishi, 1985; Nishimura et al., 1985) and dermis (Cooper et al., 1984) by using absorption promoters have been reported.

Some of possible mechanisms have been proposed: Muranushi et al. reported the enhancement of the fluidity of membranous lipid by bile acid–monoglyceride mixed micelles (Muranushi et al., 1980). Nishihata et al. (1984) suggested that some membranous proteins were related to the promotive effect of concanavalin A on the absorption of Phenol red (PR) from the rectum. Yata et al. (1985) demonstrated that the calcium chelating

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ability would be important for the promoting effect of medium chain fatty acids on the absorption of water-soluble and poorly absorbed drugs.

In our previous paper (Higaki et al., 1986), effects of medium-chain glycerides (MGK) on the intestinal absorption and biliary excretion of Bromthymol blue (BTB) have been reported. MGK emulsion caused the decrease in the accumulation of BTB into the intestinal tissue and the promotive effect on the net absorption of BTB. However, the inhibitory effect of MGK emulsion on the net absorption of the dye was observed after the pretreatment with drug-free MGK emulsion. The biliary excretion of the dye tended to decrease by the administration of MGK emulsion.

In the present study, further investigations were performed for MGK emulsion to clarify the mechanisms of its effects on the absorption and the biliary excretion of drugs, using PR as a model compound.

Materials and Methods

Materials

PR was purchased from Nakarai Chemicals, Co., Ltd. Polyoxyethylene derivatives of hydrogenated castor oil (HCO-100 and HCO-60), and MGK, a mixture of mono-, di-, tricapryl glyceride and caprylic acid, were obtained from Nikko Chemicals, Co., Ltd. All other reagents were of analytical grade and were obtained from Nakarai Chemicals, Co., Ltd. and Wako Pure Chemicals, Co., Ltd.

Preparation of drug solution

The isotonic buffer solution (pH 6.5 or pH 7.4) was prepared from 0.123 M Na_2HPO_4 and 0.163 M NaH_2PO_4. PR was dissolved in this buffer solution at a concentration of 1.0 mM.

Preparation of HCO-100 micellar solution

HCO-100, molten at 70–80 °C, was dissolved in water at 70–80 °C, cooled to room temperature, and 0.1–2.0 w/v% of HCO-100 micellar solution was prepared. Micellar solution of HCO-60 was prepared in the same way.

Preparation of MGK emulsion

HCO-100 molten at 70–80 °C was dissolved in distilled water or saline, and MGK molten at 60–70 °C and PR (1.0 mM) were added to the micellar solution in this order. The mixture was stirred magnetically and cooled to room temperature. Emulsion was also prepared using HCO-60 as an emulsifier.

Determination of free fraction of PR in MGK emulsion or micellar solution

Free fraction of PR was determined by equilibrium dialysis. Briefly, test solutions were contained inside of the cellulose tubing (Visking Company 8/32 inch, diameter = 0.6 cm) and distilled water or isotonic buffer was on the outside. The volumes of inside and outside solutions were 2 ml and 6 ml, respectively. The tubings were kept at 37 °C for 3 h with gentle shaking. After equilibration, the concentration in the outer medium was determined spectrophotometrically.

Animals

Male Wistar albino rats weighing 200–230 g were used in all experiments. During the experiments, rats were anesthetized with pentobarbital (30 mg/kg) by i.p. injection and maintained at 37 °C.

Absorption studies

In situ recirculation experiment. The intestine of the anesthetized rat was exposed through a midline incision and cannulae were inserted into the portions just after the ligament of Treitz and before the cecum. The mucosal side of the intestine was washed out twice by slowly injecting 20 ml of pH 6.5 isotonic phosphate buffer. Both cannulae were attached to the peristaltic pump, and 40 ml of a drug solution kept at 37 °C was recirculated through the intestine at a rate of 5 ml/min for 60 min. The bile duct was ligated except when bile was collected simultaneously.

In vitro everted sac experiment. A cannulated everted sac method modified (Kimura et al., 1984) from that described by Jorgensen et al. (1961) was employed. 8 cm of the jejunum or the ileum was removed from the rat, was everted and both ends of the sac were cannulated. The volumes of

mucosal and serosal solutions were 20 ml and 1.5 ml, respectively. The mucosal solution was bubbled with 95% O_2–5% CO_2 from 20 min before the start of experiments to the end. At adequate time periods, serosal samples were collected by introducing air from the upper cannula and the serosal space was successively replenished with fresh buffer solution. The experiment was performed at 37 °C with gentle shaking.

Pretreatment studies

In situ recirculation experiment. The solution for the pretreatment was perfused for 30 min in the same manner as the in situ recirculation procedure before the perfusion of test solution for 60 min.

In vitro everted sac experiment. The solution of 20 ml for the pretreatment and the buffer solution of 1.5 ml were put into the mucosal and serosal side, respectively. After the pretreatment for 10 min at 37 °C, the mucosal surface was gently washed by buffer solution and the transport study was performed for 60 min.

Absorption studies of MGK components

In situ loop method. Cannulae were inserted into the proximal and distal end of ileal segment (8 cm) before cecum. Intestinal mucosal side was gently washed out twice with 10 ml of pH 6.5 isotonic phosphate buffer. MGK emulsion was introduced into the loop and the ileal segment was put back into the peritoneal cavity. The study continued for 1 h at 37 °C.

In vitro non-everted sac experiment. 8 cm of the ileum was removed from the rat, not everted and both ends of the sac were cannulated. 1.5 ml MGK emulsion was introduced into the lumen of the ileal sac and the absorption study continued for 1 h at 37 °C. Mucosal samples were collected following the in vitro everted sac procedure.

Biliary excretion study

This study was done simultaneously with an in situ recirculation experiment. The bile duct was cannulated with polyethylene tubing (i.d. = 0.50 mm, o.d. = 0.80–0.90 mm) purchased from Dural Plastics and Engineering, Australia.

Intramesenteric venous injection study

According to the method reported by Nakae et al. (1978), 0.5 ml of MGK emulsions, HCO micellar solutions, or saline were injected into the mesenteric vein after the cannulation of bile duct. 30 s after the injection of a test solution, 1 ml PR solution was injected into the femoral vein and bile sample was collected for 90 min.

Analytical methods

PR. PR in perfused solution or serosal sample was determined spectrophotometrically at 560 nm after alkalinized with 1 N NaOH. The metabolite of PR in bile was hydrolyzed with 1 N HCl at 100 °C for 30 min and total PR in bile was measured colorimetrically at 555 nm after alkalinization with 1 N NaOH (Hart et al., 1966)

MGK components. MGK components were determined as glycerol following the methods of Van Handel et al. (1961) and Hanahan et al. (1958). After the transport experiments, the luminal solution was withdrawn and the mucosal surface was gently washed twice with 5 ml of distilled water. The washings were combined with the remaining solution and made up to 20 ml with distilled water. One ml of this mixture was shaken with $CHCl_3$ for 10 min. After evaporating $CHCl_3$ at 80 °C, 0.4 w/v% KOH–ethanol solution was added to the residue and maintained at 60–70 °C for 15 min. Then 0.2 N H_2SO_4 was added and the sample was boiled for 10 min. After cooling, 0.025 M $NaIO_4$ and 5 w/v% $NaHSO_3$ were added with 10 min reaction periods, respectively. Then chromotropic reagent was added and heated in boiling water for 30 min. After cooling, 10 w/v% thiourea was added and glycerol was measured spectrophotometrically at 570 nm.

Statistical analyses

Statistical analyses were performed using analysis of variance (ANOVA) or the Student's *t*-test to determine which differences were significant.

Results

Effect of MGK emulsion on the disappearance of PR from the intestinal lumen

The effect of MGK emulsion on the absorption of PR from the small intestine was examined with

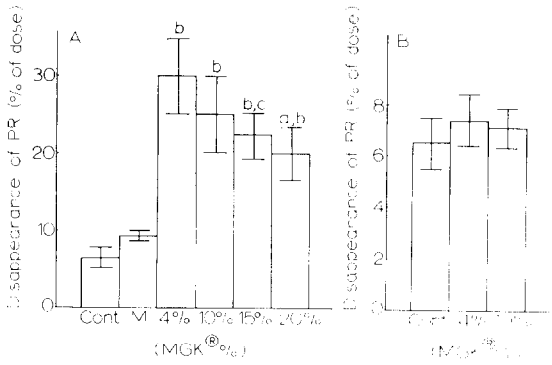

Fig. 1. Effect of MGK emulsion on the disappearance of PR during the in situ recirculation experiment for 1 h. Absorption of PR was determined from PR-containing emulsions (A) or from buffer solution after 30 min pretreatment with PR-free emulsions (B). Data are means ± S.D. of more than 4 rats. Cont. = pH 6.5 buffer solution; M. = 2% HCO-100 micellar solution. Statistically significant differences at $P < 0.05$ between two studies are indicated: a = from control, b = from micellar solution, c = from 4% MGK emulsion.

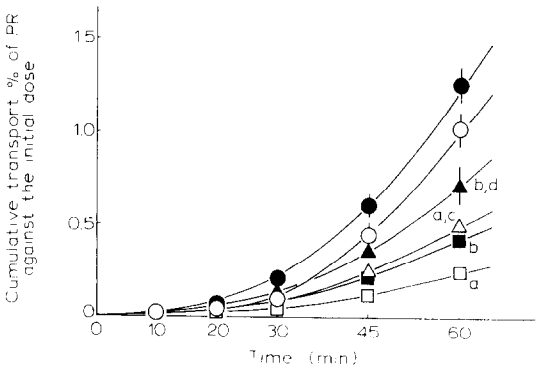

Fig. 2. Effect of MGK emulsion and HCO-100 micellar solution on the transport of PR in the everted sac experiments. Data are means ± S.D. of more than 4 rats. Statistically significant differences at $P < 0.05$ between two studies are indicated: a = from control jejunum (Jej), b = from control ileum (Ile), c = from micellar solution (Jej), d = from micellar solution (Ile): ○, control (Jej); ●, (Ile); △, 4% MGK emulsion (Jej); ▲, (Ile); □, 2% HCO-100 micellar solution (Jej); ■, (Ile).

an in situ recirculation experiment (Fig. 1A). Disappearance percent of PR from MGK emulsion was significantly greater than that from buffer solution, and MGK showed a maximum effect of over 5-fold of the control, at 4 v/v% MGK emulsion. Similar results were obtained for MGK emulsion containing HCO-60 as an emulsifier (data not shown). Fig. 1B shows the effect of pretreatment with drug-free MGK emulsion on the absorption of PR. The pretreatment with PR-free emulsions did not increase the disappearance of PR.

Effect of MGK emulsion on the transport of PR through everted intestine

An in vitro everted sac experiment was employed to investigate the effect of MGK emulsion on the transport of PR from mucosa to serosa (Fig. 2). MGK emulsion and HCO-100 micellar solution decreased PR transport in jejunum about one half and one quarter of the control, respectively. In all cases, the amount of PR transported to serosal side was greater in the ileal region than in the jejunal region. As shown in Table 1, the cumulative transport of PR in emulsions was

TABLE 1

Effect of MGK content in an emulsion on the transport of PR through everted ileum sac

Transport % are means ± S.D. of more than 4 rats. Cont. = pH 6.5 buffer solution, M. = 2% HCO-100 micellar solution. Statistically significant differences at $P < 0.05$ between two studies are demonstrated. a = from control, b = from micellar solution.

MGK %	Cumulative transport % of dose ($\times 10^{-1}$)				
	10 min	20 min	30 min	45 min	60 min
Cont.	0.07 ± 0.04	0.41 ± 0.22	1.63 ± 0.69	5.35 ± 1.19	11.50 ± 2.27
M.	0.06 ± 0.05	0.37 ± 0.15	0.93 ± 0.17 [a]	2.17 ± 0.30 [a]	4.96 ± 0.60 [a]
4%	0.11 ± 0.04	0.47 ± 0.04	1.35 ± 0.19	3.62 ± 0.78 [a,b]	7.15 ± 2.34 [a,b]
10%	0.15 ± 0.09 [a,b]	0.67 ± 0.24	1.76 ± 0.36 [b]	4.34 ± 0.78 [b]	8.49 ± 1.05 [a,b]
15%	0.13 ± 0.07 [b]	0.63 ± 0.42	1.52 ± 0.80	3.47 ± 1.29 [a,b]	7.22 ± 1.82 [a,b]

TABLE 2

Effect of HCO-100 on the transport of PR through everted jejunal sac

Transport % are means ± S.D. of more than 4 rats. Free fraction % were determined by equilibrium dialysis as shown in Materials and Methods. Statistically significant differences at $P < 0.05$ between two studies are demonstrated: a = from control, b = from 0.1% micellar solution.

HCO-100%	Cumulative transport % of dose ($\times 10^{-1}$)					Free fraction %
	10 min	20 min	30 min	45 min	60 min	
Cont.	0.04 ± 0.06	0.24 ± 0.21	0.95 ± 0.47	4.21 ± 0.86	10.20 ± 1.36	100
0.1	0.15 ± 0.05 [a]	0.68 ± 0.13 [a]	1.85 ± 0.31 [a]	4.65 ± 0.76	8.85 ± 1.32	83.55
0.5	0.05 ± 0.03 [b]	0.30 ± 0.30 [b]	1.00 ± 0.60 [b]	2.70 ± 1.10 [a,b]	5.50 ± 1.40 [a,b]	81.73
1.0	0.08 ± 0.04 [b]	0.40 ± 0.20	1.10 ± 0.30 [b]	2.60 ± 0.50 [a,b]	4.90 ± 1.00 [a,b]	77.08
2.0	0.06 ± 0.05 [b]	0.37 ± 0.15 [b]	0.93 ± 0.17 [b]	2.17 ± 0.30 [a,b]	4.14 ± 0.60 [a,b]	69.57

smaller than that of the control (buffer solution) regardless of MGK content but larger than that in micellar solution in an ileal segment.

Effect of HCO-100 on the transport of PR through everted intestine

To study mechanisms of the decrease in PR transport observed in everted sac experiments, effect of HCO-100 on the transport of PR was examined in jejunal segment (Table 2). It was observed that transport percent of PR was reduced with the increase of the content of HCO-100 and the consequent decrease of free fraction of PR in a micellar solution. Fig. 3 shows the relationship between PR transport percent and free fraction percent of PR in various formulations. In the case of MGK emulsions all points fall above the regression line for micellar solutions, which suggests that the transport of PR was promoted even in an in vitro system, too.

Effect of pretreatment with drug-free MGK emulsion on the transport of PR

Effect of pretreatment with PR-free emulsion

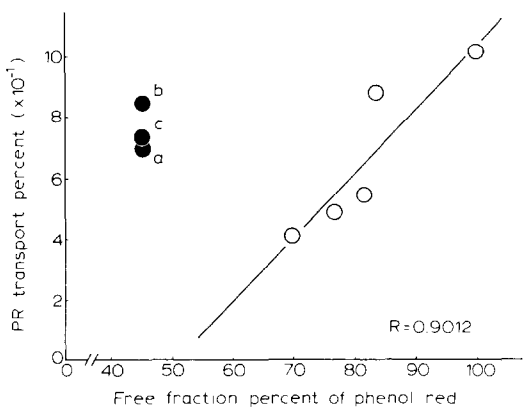

Fig. 3. Relationship of the free fraction percent of PR in micellar solution and MGK emulsion with the PR transport percent in the everted sac experiments. Data of PR transport percent were obtained from Tables 1 and 2. Free fraction percent of PR was determined by equilibrium dialysis. The straight line was obtained by a least squares method. ○, HCO-100 micellar solutions; ●, MGK emulsion; a = 4% emulsion, b = 10% emulsion, c = 15% emulsion.

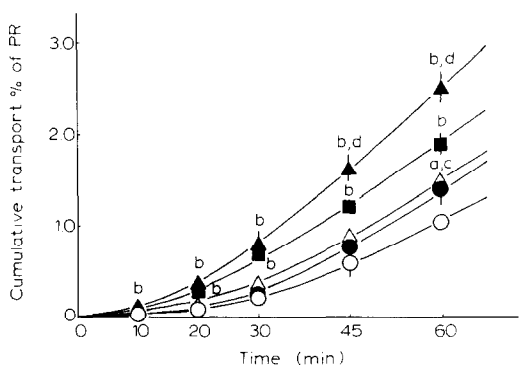

Fig. 4. Effect of pretreatment with PR-free MGK emulsion on the transport of PR through the intestinal everted sac. Transport study was started after pretreatment with PR-free MGK emulsion for 10 min. Statistically significant differences at $P < 0.05$ between two studies are indicated. a = from control (Jej), b = from control (Ile), c = from micellar solution (Jej), d = from micellar solution (Ile). ○, control (Jej); ●, (Ile); △, 4%MGK emulsion (Jej); ▲, (Ile); ■, 2% HCO-100 micellar solution (Ile).

TABLE 3

Absorption of MGK components from the ileum in the in situ loop and in vitro non-everted sac experiments

Disappearance % are shown as means ± S.D. of more than 7 rats. Experimental procedures are described in Materials and Methods. Statistically significant difference between two experimental groups are shown.

Method	Disappearance %
In situ loop	73.35 ± 6.14 [a]
In vitro non-everted sac	43.38 ± 3.15

[a] $P < 0.001$

on PR transport to serosa was investigated by in vitro everted sac experiments (Fig. 4). Pretreatment with PR-free MGK emulsion increased the transport of PR to serosa about twice of control in an ileal region. HCO-100 micellar solution also showed the same effect. In this case, the variation of a promotive effect by intestinal region was observed.

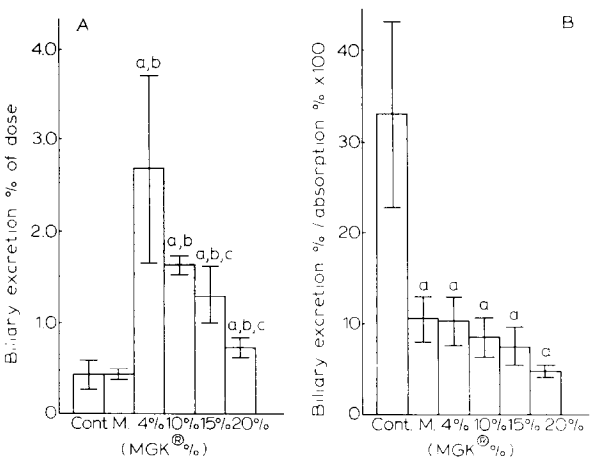

Fig. 5. Effect of MGK emulsion on the biliary excretion of PR. A: biliary excretion % of dose in the in situ recirculation study. Data are means ± S.D. of more than 3 rats. B: ratio of amount of PR excreted into bile to that absorbed from the intestine. Data were calculated from each value of A and Fig. 1A and means ± S.D. of more than 3 rats are shown. Cont. = pH 6.5 buffer solution; M = 2% HCO-100 micellar solution. Statistically significant differences at $P < 0.05$ between two studies are shown. a = from control, b = from micellar solution, c = from 4% MGK emulsion.

Absorption of MGK components

To examine the difference of MGK effect between in vitro and in situ loop experiments, the absorption of MGK components in an emulsion was investigated in both systems. As shown in Table 3, disappearance percent of MGK components was about twice as large for in situ study as for in vitro study.

Effect of MGK emulsion on the biliary excretion of PR

Fig. 5A shows cumulative biliary excretion of PR when PR emulsion was perfused through the rat small intestine. Although excretion percent of PR was increased comparing with the buffer solution (control), the ratio of the biliary excretion percent to the absorption (disappearance) percent (B/A ratio) shown in Fig. 5B was smaller than that of the control. Similar data were obtained in the experiment using HCO-60 as an emulsifier (data not shown).

Effect of the injection of MGK emulsion components into the mesenteric vein on the biliary excretion of PR

Biliary excretion of PR was below the control value when 1–4% MGK emulsions or 2% HCO-60

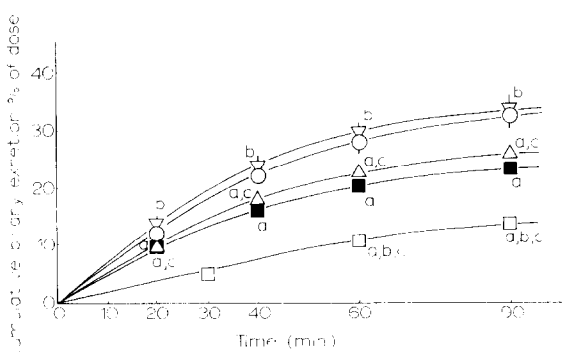

Fig. 6. Effect of MGK emulsion components injected into the mesenteric vein on the biliary excretion of PR. Experimental procedures are described in Materials and Methods. Data are means ± S.D. of more than 4 rats. Statistically significant differences at $P < 0.05$ between two studies are shown. a = from control, b = from micellar solution, c = from 0.5% emulsion. ○, control (saline); □, 4% MGK emulsion; △, 1% MGK emulsion; ▽, 0.5% MGK emulsion; ■, 2% HCO-60 micellar solution.

micellar solution was injected into the mesenteric vein before the injection of PR (Fig. 6).

Discussion

Lipoidal preparations have been widely studied to modify a drug absorption in gastrointestinal tract including rectum (Muranishi, 1985; Nishimura et al., 1984) and dermis (Cooper et al., 1984). Although various hypotheses were offered for these adjuvants (Muranishi, 1985; Muranushi et al., 1980; Yata et al., 1985; Nishihata et al., 1985; Shiga et al., 1986), few definitive mechanisms have been established. MGK is one of the adjuvants, the mechanism of which remains to be elucidated.

The previous paper presented the effect of MGK emulsion on the absorption and hepatobiliary transport of BTB (Higaki et al., 1986). In the present study PR, which is poorly absorbed from the gastrointestinal tract (Nakamura et al., 1976 a and b) and excreted actively into bile (Guarino et al., 1976), was employed as another model dye and the effects of MGK were investigated. Although the absorption of BTB was not extensively promoted by MGK emulsion (Higaki et al., 1986), that of PR for emulsion was over 5 times as large as control in the in situ recirculation experiment (Fig. 1A). The disappearance percent of PR was maximum at a MGK content of 4% and decreased with the increase of MGK content in an emulsion. This result suggests that MGK has both enhancing and inhibiting effects on PR absorption being in good agreement with the results reported by Sekine et al. (1984). The result of pretreatment with drug-free MGK emulsion (Fig. 1B) would approve the conclusion of a previous paper (Higaki et al., 1986) as the promoting effect of MGK emulsion demands the coexistence of MGK with the dyes.

The differences between the effect of MGK on intestinal absorption of PR and BTB would be attributed to their physicochemical properties. The extensive accumulation of BTB in the intestinal tissue (Nakamura et al., 1976b) and the interaction with MGK emulsion seemed to have a close relationship to its absorption but they are not explained by its lipophilicity (Higaki et al., 1986). Table 4 summarized the effects of MGK emulsion on PR and BTB. PR which exists in water phase of the emulsion at a higher extent was more efficiently absorbed than BTB. This result would be reasonable from the general concept of drug absorption from an emulsion that drugs released from oil droplets of an emulsion are absorbed (Ogata et al., 1975).

TABLE 4

Comparison of MGK action on BTB and PR

Absorption studies were carried out by an in situ recirculation for 1 h. Data are means ± S.D. of more than 4 rats. Free fraction % were determined by equilibrium dialysis.

Model dyes	Disappearance % of dose		Free fraction %
	Control	4% MGK emulsion	
BTB	4.83 ± 2.64 [a]	7.52 ± 0.27 [a]	4.34
PR	6.50 ± 1.74	30.10 ± 4.88	45.22

[a] Net absorption %.

A contradictory result was observed in the experiment using everted intestinal sacs (Fig. 2). In this system, both MGK emulsion and a micellar solution suppressed the absorption of PR. Moreover, the increment of MGK content in an emulsion could not promote the absorption of PR (Table 1). Although the promotive effect of MGK emulsion on PR absorption was apparently deleted in an in vitro system, the relationship between transport percent and free fraction percent of PR (Fig. 3) showed that MGK emulsion should contribute to the PR transport since transport percent of PR exceeded that expected from the free drug content. As compared to HCO-100 micellar solutions, also membrane permeability was enhanced by this system by the pretreatment with drug-free emulsion (Fig. 4). Consequently, in addition to the membrane permeability problem, the dynamic movement of a solute from MGK formulation was considered to be affected with various factors such as presence or absence of blood flow (Binns, 1964), neurohumoral control (Berridge, 1983), transport of water (Berridge, 1983; Ochsenfahrt et al., 1974), and the distance of passage route (Wolfe et al., 1973).

Disappearance of MGK in the in situ experiment was about twice of that in the vitro experiment (Table 3). Although it is uncertain whether the change of MGK absorption itself or some factors affecting the absorption of MGK is important for the movement of a solute, the absorption of MGK seemed to be related to the enhancement of PR absorption because the coexistence of MGK with the solute was demonstrated to be necessary for the promotive effect of MGK.

It was reported that absorption of MGK was decreased to one third without lipase (Clark et al., 1968). Since the bile duct was ligated in the in situ loop experiment, pancreatic lipase was not supplied into the intestinal tract under this condition, although membraneous lipase (Playoust et al., 1964) might be secreted in this system more than in the in vitro system. Blood flow (Csasky, 1984) and neurohumoral control (Cooke, 1984), moreover, were suggested to influence the intestinal transport of nutrients.

As far the membrane permeability, caprylic acid, one of components and metabolic products of MGK, was reported to affect the membrane fluidity (Kajii et al., 1985) and to have a chelating ability (Yata et al., 1983). Therefore, MGK emulsion might have these effects on intestinal membrane. However additional studies would be necessary to elucidate the action of glycerylcaprylates which have different physicochemical properties from caprylate.

Effects of MGK on the biliary excretion have also been examined in the case of PR (Fig. 5B). Although the amount of PR excreted into bile was increased (Fig. 5A) with the increment of absorbed amount, B/A ratio was significantly decreased. The suppression of biliary excretion would be concerned with the components of MGK absorbed and transferred to the liver. The effect of MGK components, therefore, was directly investigated by employing the intramesenteric venous injection method (Fig. 6). As shown in Fig. 6, MGK components except of 0.5% MGK emulsion injected into mesenteric vein inhibited the excretion of PR into bile suggesting that MGK components absorbed from the intestinal tract could affect the biliary excretion of PR in the in situ study. Although most MGK was reported to be absorbed after metabolism to free fatty acid and glycerol in the intestinal lumen (Greenberger et al., 1969), some MGK components should be transported to the mesenteric vein without metabolic degradation in the absence of pancreatic lipase (Johnson, 1981). The result of an in situ study, therefore, would be simulated by the intramesenteric venous injection study. Takada et al. (1978) reported that absorbed tricaprylate could inhibit the active excretion process of anionic chemicals from hepatocytes to the bile. Band III protein, which plays an important role on the active biliary excretion of organic anions, was reported to be solubilized by intraduodenal administration of tricaprylate and excreted into the bile (Takada et al., 1976). If PR and its metabolites could be excreted via this transport system, MGK components should have an effect on this transport system in the same way.

In the present study, several important suggestions on the effect of MGK on the absorption and the biliary excretion of PR were raised. However, each of several components will require an extensive research before the total performance of MGK can be identified.

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