

Full Paper

Effect of Mosapride Citrate Hydrate on the Colon Cleansing Action of Polyethylene Glycol Electrolyte Lavage Solution (PEG-ELS) in Guinea PigsYukiko Mine^{1,*}, Kazuo Morikage², Seiko Oku¹, Takashi Yoshikawa³, Isao Shimizu¹, and Naoyuki Yoshida¹¹Discovery Pharmacology II, Pharmacology Research Laboratories, Dainippon Sumitomo Pharma Co., Ltd., 33-94 Enoki-cho, Suita, Osaka 564-0053, Japan²Animal Health Products Group, Non-Pharmaceutical Operations, Dainippon Sumitomo Pharma Co., Ltd., 5-51, Ebie 1-chome, Fukushima-ku, Osaka 553-0001, Japan³Drug Development Division, Dainippon Sumitomo Pharma Co., Ltd., 6-8 Doshomachi 2-Chome, Chuo-ku, Osaka 541-0045, Japan

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Abstract. Polyethylene glycol electrolyte lavage solution (PEG-ELS) is widely used for colon cleansing prior to colonoscopy and colonic surgery. It has recently been shown that coadministration of PEG-ELS and mosapride citrate hydrate (mosapride), a selective 5-HT₄-receptor agonist, is clinically useful for barium enema examination as it allows adequate barium coating. However, there is no report showing that mosapride has beneficial effects on colon cleansing and its underlying mechanism in experimental animals. In the present study, we investigated the effects of mosapride on colonic transit and on the colon cleansing action of PEG-ELS in guinea pigs. Mosapride (10 – 20 mg/kg, i.g.) significantly enhanced colonic transit rate in guinea pigs. Although PEG-ELS alone showed adequate colon cleansing action, excess fluid remained in the colon. Coadministration of mosapride (20 mg/kg) and PEG-ELS, regardless of mosapride timing, reduced colonic content weight (dry residue and water amount) as compared to PEG-ELS alone. These findings suggest that mosapride enhances the colon cleansing action of PEG-ELS via an increase in colonic transit in guinea pigs, that is, it reduces not only fecal residue but also excessive fluid in the colonic lumen. It is therefore believed that coadministration of mosapride and PEG-ELS can allow better visualization in barium enema examination.

Keywords: mosapride citrate hydrate, 5-HT₄-receptor agonist, polyethylene glycol electrolyte lavage solution (PEG-ELS), colonic transit, colon cleansing

Introduction

Adequate colon preparation before diagnostic and therapeutic procedures is important because diagnosis accuracy and patient safety depend on adequate visualization. In the case of barium enema examination, a combination of laxatives, such as sennoside, and adequate diet (named Brown's method) is commonly used. However, the cleansing effect of this combination is unsatisfactory, in addition to the facts that dietary

restriction from the previous day is a burden for patients. Consequently, new methods of colon preparation for barium enema examination have long been investigated.

Polyethylene glycol electrolyte lavage solution (PEG-ELS), which was introduced by Davis et al. back in 1980, has widely been used for colon cleansing prior to colonoscopy and colonic surgery (1, 2). PEG-ELS has an adequate colon cleansing effect with little absorption of water or electrolytes. However, in the case of barium enema examination, the use of PEG-ELS is inappropriate due to poor mucosal coating caused by retention of excess fluid in the colon lumen (3, 4). Therefore, various methods have clinically been investigated in order to reduce this retention of lavage solution

*Corresponding author. yukiko-mine@ds-pharma.co.jp
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(5, 6). As a result, it has been reported that coadministration of cisapride, a 5-HT₄-receptor agonist, and PEG-ELS is a useful method to ensure appropriate colon cleansing and to reduce both lavage solution volume and residual water (6–8). However, cisapride has been withdrawn from the market because of severe cardiac side effects including QT-interval prolongation and ventricular arrhythmias (9). As mosapride citrate hydrate (mosapride), another 5-HT₄-receptor agonist, has been shown to have little effect on QT-interval (10), its coadministration with PEG-ELS has been investigated.

Actually, it is suggested that coadministration of mosapride and PEG-ELS is useful in preparing the colon for barium enema examination as it allows good assessment of the amount of remaining feces and adequate barium coating (11). It is thus believed that the improving effect of mosapride on the cleansing action of PEG-ELS is due to its enhancing effect on colonic motility and transit. However, there is no report showing that mosapride has beneficial effects on colon cleansing and its underlying mechanism in experimental animals. Therefore, in the present study, we investigated the effect of mosapride on colonic transit and on the colon cleansing action of PEG-ELS by evaluating the weight of the colonic contents in guinea pigs. Moreover, a clinical study has shown that administration of mosapride before and after administration of PEG-ELS results in better colon preparation than single administration of mosapride before or after PEG-ELS (11). Therefore, we examined in this study the effect of mosapride, given at different regimens, on the colon cleansing action of PEG-ELS in guinea pigs.

Materials and Methods

Animals

Male guinea pigs of the Hartley strain (Japan SLC, Inc., Shizuoka) weighing 250–400 g were used. Animals were housed in stainless steel cages in pairs before the surgical operation and individually housed after the operation. All animals were maintained in a temperature (23 ± 3°C)- and humidity (55 ± 15%)-controlled animal room under a 12:12 h light-dark cycle. Standard food (RC4; Oriental Yeast Co., Ltd., Tokyo) and tap water were available ad libitum. All experiments in this study were approved by the Institutional Animal Care and Use Committee at the Drug Research Division, Dainippon Sumitomo Pharma Co., Ltd.

Drugs

Mosapride {(±)-4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl] benzamide citrate dehydrate} was synthesized in our laboratories. Other

compounds used in this study were purchased commercially: PEG-ELS (Niflec[®]; AJINOMOTO PHARMA Co., Ltd., Tokyo), Evans blue (Nacalai Tesque Co., Ltd., Kyoto), metoclopramide hydrochloride (Sigma Chemical Co., St. Louis, MO, USA). Mosapride and metoclopramide were suspended in 0.5% tragacanth gum aqueous solution. The concentration of mosapride was expressed as an equivalent of mosapride in its anhydrous form. Each pack of Niflec[®] (137.155 g), containing NaCl (2.93 g), KCl (1.485 g), NaHCO₃ (3.37 g), Na₂SO₄ (11.37 g), and polyethylene glycol 4000, was dissolved in 2 L purified water. Evans blue was suspended in 1.5% CMC (Carboxymethyl Cellulose Sodium Salt) aqueous solution at a concentration of 2.5%.

Animals preparation

Guinea pigs were anesthetized with sodium pentobarbital (Nembutal[®], 35 mg/kg, i.p.; Dainippon Sumitomo Pharma Co., Ltd., Osaka), and the abdomen was opened by midline laparotomy. A polyethylene tube (I.D. of 0.5 mm, O.D. of 0.8 mm, 15 cm) was inserted into the gastric body for drug administration (mosapride, vehicle, and PEG-ELS). For colonic transit experiments, a silicon tube (I.D. of 1.0 mm, O.D. of 2.0 mm, 15 cm) was inserted into the colon for injection of Evans blue (2.5%) in addition to the intragastric tube. In brief, a small incision was made into the cecum (1-cm proximal to the cecocolic junction), and a silicon tube was implanted through it and its tip was positioned in the proximal colon (2-cm distal to the cecocolic junction). These tubes in the abdominal cavity were brought out through a skin incision made between the scapulae, and the skin incisions in the abdomen and the back were sutured. The tube was filled with purified water and its outlet was blocked with a plastic stopper. Animals were then individually housed in stainless steel cages until the experiment. All experiments in this study were performed under unfasted conditions because the content of the cecum in guinea pigs is so large that there was incomplete emptying of the colonic content even if the animals fasted for 24 h.

Colonic transit in guinea pigs

On the 4th day after the surgical operation, unfasted guinea pigs were intragastrically administered mosapride or its vehicle (2 mL/kg). Thirty minutes later, 1 mL Evans blue (2.5%) was injected into the proximal colon through an indwelling tube. Animals were sacrificed by a blow on the head 30 min after administration of Evans blue, and the entire colon, from the cecocolonic junction to the distal end of the colon, was surgically removed. The full length of the colon and the distance traversed by Evans blue were then measured. Colonic transit was

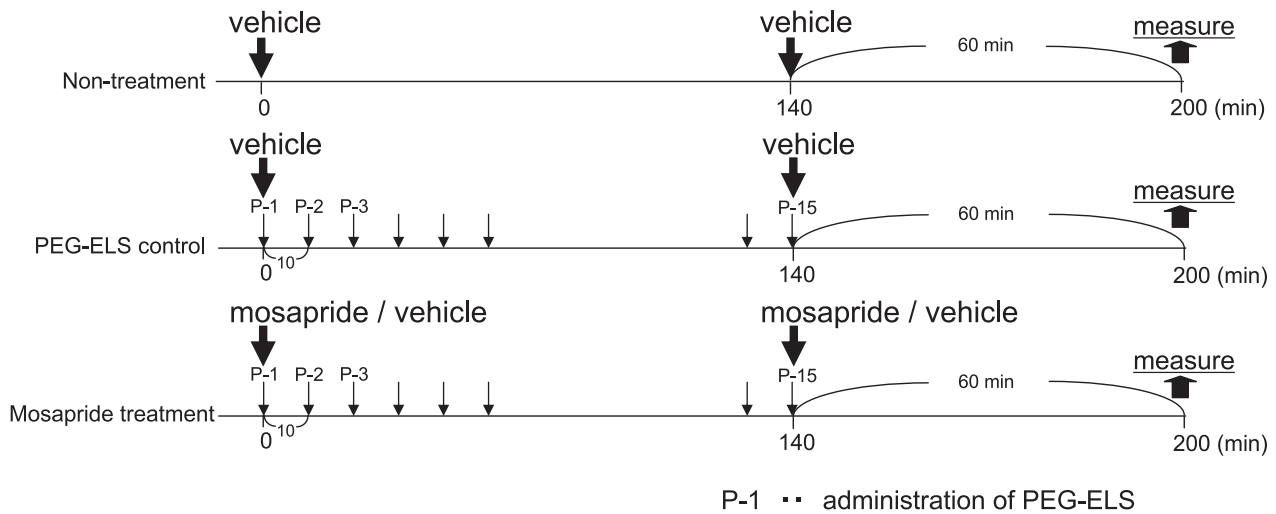


Fig. 1. Schematic representation of protocol for the colon cleansing experiments. PEG-ELS solution (20 mL/kg) was intragastrically administered to guinea pigs 15 times at intervals of 10 min. Mosapride or vehicle (2 mL/kg) was intragastrically administered at the start (0 min) and/or at the end (140 min) of PEG-ELS administration. Animals were sacrificed 60 min after the last dosing with mosapride or vehicle.

expressed as the percentage of distance traversed by Evans blue to the total length of the colon.

Colon cleansing action of PEG-ELS in guinea pigs

On the 4th day after the surgical operation, PEG-ELS and mosapride (or vehicle) were administered to unfasted guinea pigs. The administration schedule is shown in detail in Fig. 1 and can be summarized as follows: PEG-ELS (20 mL/kg) was intragastrically administered to guinea pigs 15 times at intervals of 10 min. Mosapride or vehicle (2 mL/kg) was intragastrically administered at the start (0 min) and/or at the end (140 min) of PEG-ELS administration. Animals were sacrificed by a blow on the head 60 min after the last dosing with mosapride or vehicle. The cecocolonic junction and distal end of the colon were ligated, and the colon was removed. The whole colon including its content was weighed (weight A). The colon was then longitudinally cut open and its content was extracted on a pre-weighed filter paper (weight B). The net weight of the colon without its content was measured after washing and wiping (weight C). Finally, the extracted colonic content and the pre-weighed filter paper were dried and weighed (weight D).

Weight of the extracted dry colonic content (X) and that of water in the colonic content (Y) were calculated as follows: $X = D - B$, $Y = (A - C) - (D - B)$, where A = weight of whole colon including its content, B = weight of filter paper, C = weight of colon without its content, and D = weight of dried colonic content + weight of the filter paper.

Statistical analyses

The results are expressed as the mean \pm S.E.M. Statistical analysis was performed by using the SAS system (version 6.12; SAS Institute, Inc., Cary, NC, USA) and SAS Application for Preclinical Study Version 4.1 (SAS Institute Japan, Ltd., Tokyo). Values of $P < 0.05$ were considered as statistically significant. In the colonic transit experiment, differences between the vehicle control group and each mosapride-treated group were analyzed by Dunnett's multiple comparison test. Linearity of the dose-response for colonic transit was examined by linear regression analysis. In the colon cleansing experiments, differences in the weight of dry colonic content between the non-treatment group and PEG-ELS control group were analyzed using Student's *t*-test. In the case of a significant decrease in the weight of dry colonic content in the PEG-ELS control group, differences in each weight of colonic content (dry residue or water amount) between the PEG-ELS control group and each mosapride treatment group were analyzed by Dunnett's multiple comparison test. Linearity of the dose-response for the weight of colonic content was examined by linear regression analysis.

Results

Effect of mosapride on colonic transit in guinea pigs

As shown in Fig. 2, colonic transit in the vehicle control group was $34.63 \pm 5.95\%$. Intragastric administration of mosapride at 10 and 20 mg/kg significantly enhanced colonic transit to $58.67 \pm 8.83\%$ ($P = 0.0389$).

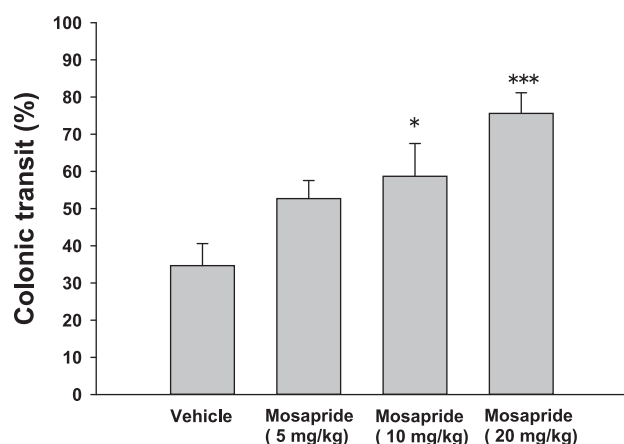


Fig. 2. Effect of mosapride on colonic transit in guinea pigs. Each column represents the mean \pm S.E.M. of colonic transit ($n = 7-9$). Mosapride or vehicle was intragastrically administered to guinea pigs. Thirty minutes later, Evans blue (2.5%) was instilled into the proximal colon through an indwelling tube. Animals were sacrificed 30 min after administration of Evans blue, and the distance traversed by Evans blue was measured and its ratio to the full length of the colon was calculated. * $P < 0.05$, *** $P < 0.001$, significantly different from the vehicle control group (Dunnett's multiple comparison test).

and $75.60 \pm 5.52\%$ ($P = 0.0008$), respectively. In addition, the effect of mosapride (5, 10, and 20 mg/kg) on colonic transit was linearly related to the dose (linearity: $P = 0.0285$ and non-linearity: $P = 0.8454$), indicating that mosapride dose-dependently enhances colonic transit in guinea pigs.

Colon cleansing action of PEG-ELS or mosapride in guinea pigs

First of all, we examined the colon cleansing effect of mosapride alone in guinea pigs. As shown in Fig. 3, mosapride, given at 10 mg/kg, had no significant effect on the weight of dry colonic content or that of water in the colonic content. As shown in Figs. 3–7, PEG-ELS, given intragastrically to guinea pigs 15 times at intervals of 10 min, significantly reduced the weight of dry colonic content as compared with that in the non-treatment group, confirming the colon cleansing action of PEG-ELS in guinea pigs. On the other hand, PEG-ELS did not reduce the weight of water in the colonic content as compared with that in the non-treatment group.

Effect of mosapride (5–20 mg/kg), given at the start of PEG-ELS administration, on the weight of dry colonic content and that of water in the total colonic contents in guinea pigs

As shown in Fig. 4, in the guinea pigs treated with mosapride (20 mg/kg, i.g.) at the start (0 min) of PEG-ELS administration, the weight of dry colonic content and that of water in the total colonic contents were significantly lower than those in the PEG-ELS control group ($P = 0.003$ and $P = 0.0036$, respectively). In addition, there was a linear relationship between the dose of mosapride (5–20 mg/kg) and its reducing effect on the weight of colonic content (dry weight,

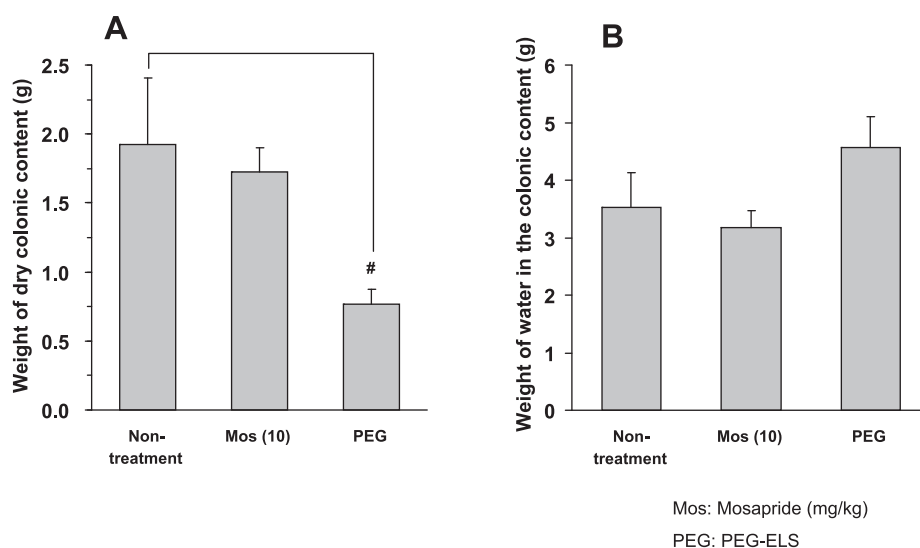


Fig. 3. Effect of mosapride (10 mg/kg) or PEG-ELS on the weight of dry colonic content (A) and that of water in the colonic content (B). Each column represents the mean \pm S.E.M. of the weight of colonic content ($n = 6$). In the non-treatment group, vehicle was administered to the guinea pigs. In the mosapride group, mosapride (10 mg/kg, i.g.) was administered to the guinea pigs. In the PEG-ELS group, PEG-ELS solution (20 mL/kg) was intragastrically administered to the guinea pigs 15 times at intervals of 10 min. Animals were sacrificed 60 min after the last dosing with PEG-ELS, mosapride, or vehicle, and their colonic contents were weighed. # $P < 0.05$, significantly different from the non-treatment group (Student's t -test).

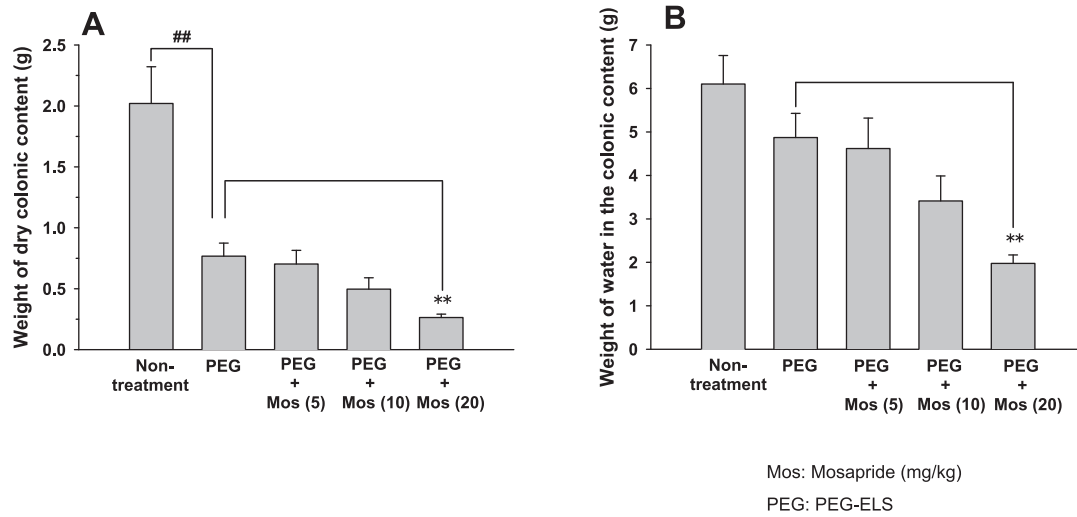


Fig. 4. Effect of mosapride (5–20 mg/kg), given at the start of PEG-ELS administration, on the weight of dry colonic content (A) and that of water in the colonic content (B). Each column represents the mean \pm S.E.M. of the weight of colonic content ($n = 7-9$). PEG-ELS solution (20 mL/kg) was intragastrically administered to guinea pigs 15 times at intervals of 10 min. Mosapride (5, 10, and 20 mg/kg, i.g.) or vehicle was given at the start (0 min) of PEG-ELS administration. Animals were sacrificed 200 min after dosing with mosapride or vehicle, and their colonic contents were weighed. In the non-treatment group, only vehicle was administered to guinea pigs. $^{\#}P < 0.01$, significantly different from the non-treatment group (Student's *t*-test). $^{**}P < 0.01$, significantly different from the PEG-ELS control group (Dunnett's multiple comparison test).

linear regression: $P = 0.0035$ and deviations from linearity: $P = 0.5892$; water weight, linear regression: $P = 0.0045$ and deviations from linearity: $P = 0.6360$).

Effect of mosapride (20 mg/kg), given at different regimens with PEG-ELS administration, on the weight of dry colonic content and that of water in the total colonic contents in guinea pigs

As shown in Fig. 5, in the guinea pigs treated once with mosapride (20 mg/kg) either at the start (0 min) or at the end (140 min) of PEG-ELS administration, the weight of dry colonic content and that of water in the total colonic contents were significantly lower than those in the PEG-ELS control group. Similarly, in the guinea pigs treated twice with mosapride [10 mg/kg at the start (0 min) and 10 mg/kg at the end (140 min) of PEG-ELS administration], the weight of dry colonic content and that of water in the total colonic contents were significantly lower than those in the PEG-ELS control group.

Effect of mosapride (10 mg/kg), given at different regimens with PEG-ELS administration, on the weight of dry colonic content and that of water in the total colonic contents in guinea pigs

As shown in Fig. 6, in the guinea pigs treated once with mosapride (10 mg/kg) at the end (140 min) of PEG-ELS administration, the weight of dry colonic

content was significantly lower than that in the PEG-ELS control group ($P = 0.0303$). In addition, in the guinea pigs treated twice with mosapride [5 mg/kg, each time; at the start (0 min) and at the end (140 min) of PEG-ELS administration], the weight of dry colonic content and that of water in the total colonic contents were significantly lower than those in the PEG-ELS control group ($P = 0.0243$ and $P = 0.0371$, respectively). On the other hand, in the guinea pigs treated once with mosapride (10 mg/kg) at the start (0 min) of PEG-ELS administration, neither the weight of dry colonic content nor that of water in the total colonic contents was significantly lower than that in the PEG-ELS control group.

Effect of metoclopramide (50 mg/kg) or mosapride (20 mg/kg), given at the start of PEG-ELS administration, on the weight of dry colonic content and that of water in the total colonic contents in guinea pigs

As shown in Fig. 7, in the guinea pigs treated with metoclopramide (50 mg/kg) or mosapride (20 mg/kg) at the start (0 min) of PEG-ELS administration, the weight of dry colonic content and that of water in the total colonic contents were significantly lower than those in the PEG-ELS control group (dry weight, metoclopramide: $P = 0.0028$ and mosapride: $P = 0.0049$; water weight, metoclopramide: $P = 0.0016$ and mosapride: $P = 0.0017$).

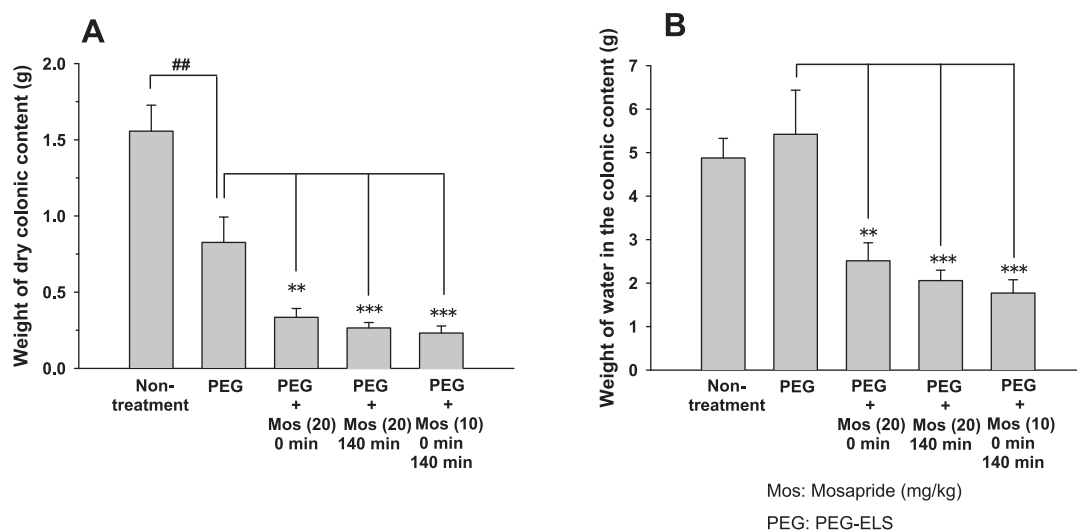


Fig. 5. Effect of mosapride (20 mg/kg), given at different regimens with PEG-ELS administration, on the weight of dry colonic content (A) and that of water in the colonic content (B) in guinea pigs. Each column represents the mean \pm S.E.M. of the weight of colonic content ($n = 8 - 9$). PEG-ELS solution (20 mL/kg) was intragastrically administered to guinea pigs 15 times at intervals of 10 min. Mosapride (20 mg/kg, i.g.) was given once either at the start (0 min) or at the end (140 min) of PEG-ELS administration, or it was given twice (10 mg/kg, i.g., each time) at the start (0 min) and at the end (140 min) of PEG-ELS administration. Animals were sacrificed 60 min after the last dosing with mosapride or vehicle, and their colonic contents were weighed. In the non-treatment group, only vehicle was administered to guinea pigs. $^{##}P < 0.01$, significantly different from the non-treatment group (Student's *t*-test). $^{**}P < 0.01$, $^{***}P < 0.001$, significantly different from the PEG-ELS control group (Dunnett's multiple comparison test).

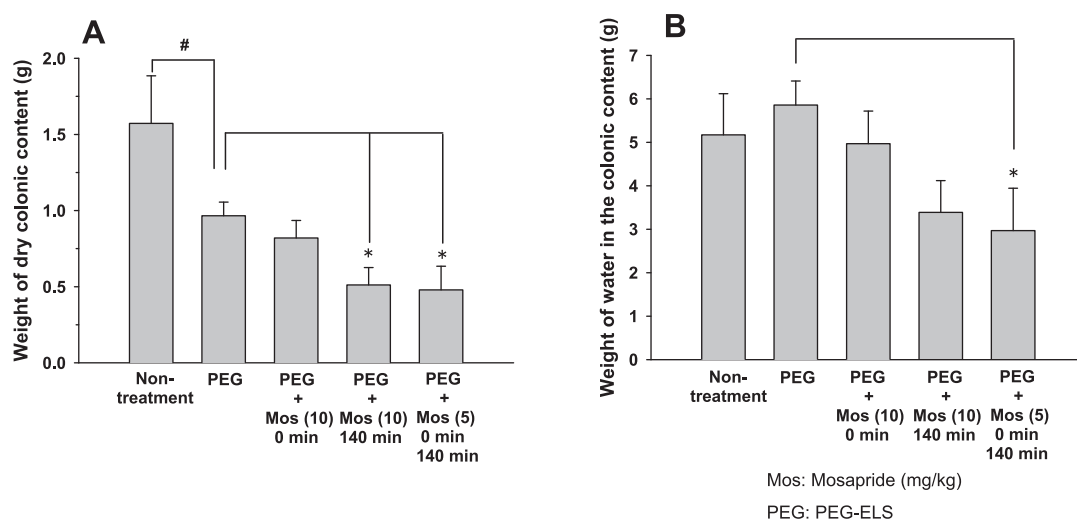


Fig. 6. Effect of mosapride (10 mg/kg), given at different regimens with PEG-ELS administration, on the weight of dry colonic content (A) and that of water in the colonic content (B) in guinea pigs. Each column represents the mean \pm S.E.M. of the weight of colonic content ($n = 7 - 9$). PEG-ELS solution (20 mL/kg) was intragastrically administered to guinea pigs 15 times at intervals of 10 min. Mosapride (10 mg/kg, i.g.) was given once either at the start (0 min) or at the end (140 min) of PEG-ELS administration, or it was given twice (5 mg/kg, i.g., each time) at the start (0 min) and the end (140 min) of PEG-ELS administration. Animals were sacrificed 60 min after the last dosing with mosapride or vehicle, and their colonic contents were weighed. In the non-treatment group, only vehicle was administered to guinea pigs. $^{#}P < 0.05$, significantly different from the non-treatment group (Student's *t*-test). $^{*}P < 0.05$, significantly different from the PEG-ELS control group (Dunnett's multiple comparison test).

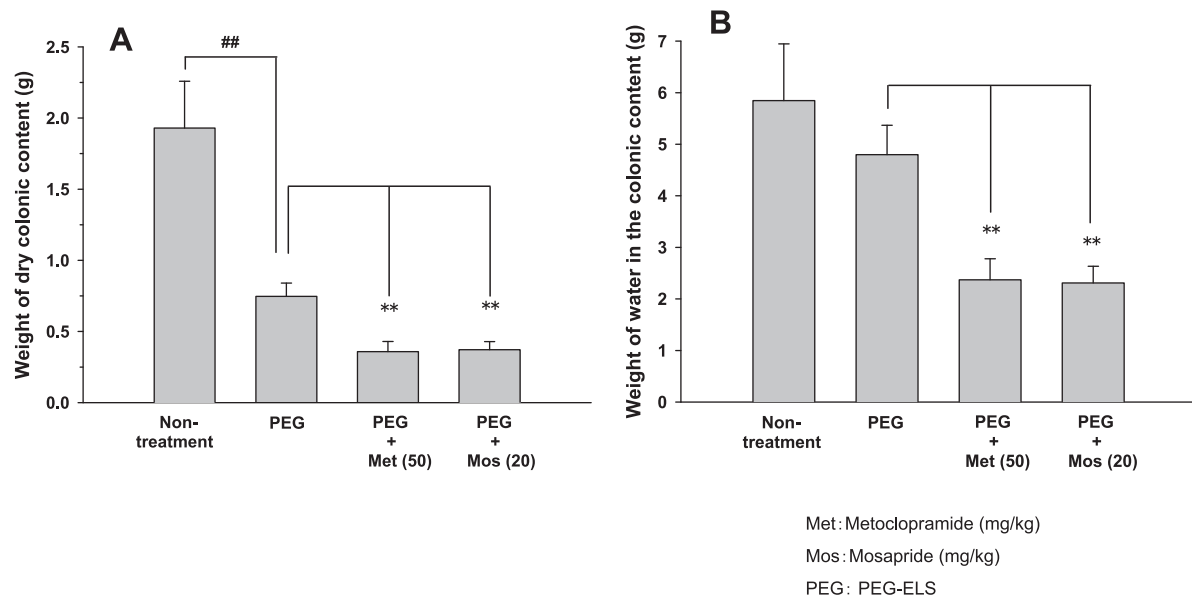


Fig. 7. Effect of metoclopramide (50 mg/kg) or mosapride (20 mg/kg), given at the start of PEG-ELS administration, on the weight of dry colonic content (A) and that of water in the colonic content (B). Each column represents the mean \pm S.E.M. of the weight of colonic content ($n = 7-9$). PEG-ELS solution (20 mL/kg) was intragastrically administered to guinea pigs 15 times at intervals of 10 min. Metoclopramide (50 mg/kg, i.g.), mosapride (20 mg/kg, i.g.), or vehicle was given at the start (0 min) of PEG-ELS administration. Animals were sacrificed 200 min after dosing with metoclopramide, mosapride, or vehicle, and their colonic contents were weighed. In the non-treatment group, only vehicle was administered to guinea pigs. $^{##}P < 0.01$, significantly different from the non-treatment group (Student's *t*-test). $^{**}P < 0.01$, significantly different from the PEG-ELS control group (Dunnett's multiple comparison test).

Discussion

Mosapride is a gastroprokinetic agent indicated for the treatment of gastrointestinal (GI) symptoms associated with chronic gastritis and functional dyspepsia (12–15). It has been reported that mosapride increases gastric emptying in rats and human (16, 17) and enhances motility in the upper GI tract of conscious dogs (12, 18). Recent studies have indicated that 5-HT₄ receptors are present in the myenteric plexus and the muscle of the stomach and colon of both humans and guinea pigs (19, 20). Additionally, using receptor autoradiograms, it was shown that mosapride has high affinity for 5-HT₄ receptors in the colons of guinea pigs (21). In the same study, it was also demonstrated that mosapride enhances colonic motility in conscious guinea pigs and that this effect is antagonized by atropine or a selective 5-HT₄-receptor antagonist (21). Moreover, it has been reported that mosapride may be effective against constipation in patients with dysfunction of lower GI motility (22). These findings suggest that mosapride enhances colonic motility in guinea pigs and humans by stimulating the 5-HT₄ receptor and thereby increasing acetylcholine release from nerve endings. However, it is unclear whether mosapride has beneficial effects on colonic transit rate, which is important in the transportation of

colonic contents. To clarify this point, we investigated the effect of mosapride on colonic transit in guinea pigs.

Our results show that mosapride dose-dependently enhances colonic transit rate in guinea pigs with a significant effect at doses of 10 and 20 mg/kg (Fig. 2). It is reported that mosapride administered intragastrically at doses of 3–30 mg/kg significantly enhances colonic motility in conscious guinea pigs implanted with force transducers (21). It is also reported that mosapride accelerates proximal and distal colonic transit or peristalsis in vitro in guinea pigs (23). These results indicate that the stimulatory effect of mosapride on colonic transit is due to accelerated colonic motility and peristalsis in guinea pigs. Next, we investigated whether mosapride can enhance the colon cleansing action of PEG-ELS via stimulation of colonic transit in guinea pigs.

Clinically, about 2,000 mL of PEG-ELS is usually required for adequate bowel preparation. In this study in guinea pigs, PEG-ELS (20 mL/kg) was intragastrically administered 15 times at intervals of 10 min as described in a reference study in rats or dogs (2). Actually, in the PEG-ELS control group in this study, the weight of dry colonic content was significantly lower than that in the non-treatment group (Figs. 3–7). This result confirms that PEG-ELS has an adequate colon cleansing action in

guinea pigs as well as in humans (4). However, the weight of water in the colonic contents in the PEG-ELS control group was not reduced as compared with that in the non-treatment group. In the non-treatment group, water in the colonic contents is considered to be the amount of moisture contained in residual stool. In the PEG-ELS control group, on the other hand, it is thought that water in the colonic contents derives mainly from the lavage solution, that is, PEG-ELS itself. These results are similar to those of a clinical study showing that the lavage solution remains in the colonic lumen. Therefore, we investigated whether mosapride can enhance the colon cleansing action of PEG-ELS and/or reduce the retention of lavage solution in guinea pigs.

First of all, we investigated the effect of mosapride, given at the start of PEG-ELS administration, on the colon cleansing action of PEG-ELS in guinea pigs (Fig. 4). This study shows that coadministration of mosapride (5–20 mg/kg) and PEG-ELS dose-dependently reduced colonic contents weight (dry residue and water amount) as compared to PEG-ELS alone with significant effect at the dose of 20 mg/kg. These results indicate that mosapride enhances the colon cleansing action of PEG-ELS and reduces excessive fluid in the colonic lumen. Our results also show that mosapride (10 and 20 mg/kg) significantly enhances colonic transit in guinea pigs and that the effective dose-range for this enhancement is similar to that used to enhance the colon cleansing action of PEG-ELS. From these findings, it is suggested that the enhancing effect of mosapride on the colon cleansing action of PEG-ELS is caused by its enhancement of colonic transit.

Secondly, we examined in this study the effect of mosapride, given at three different regimens, on the colon cleansing action of PEG-ELS in guinea pigs. Namely, mosapride was given once, either at the start or at the end of PEG-ELS administration, or it was given twice (at the start and at the end of PEG-ELS administration). In the guinea pigs treated once with mosapride (20 mg/kg), either at the start or at the end of PEG-ELS administration, or twice [10 mg/kg, each time; at the start and at the end of PEG-ELS administration], the weight of dry colonic content and that of water in the total colonic contents were significantly reduced as compared with those in the PEG-ELS control group (Fig. 5). These results indicate that administration of mosapride at 20 mg/kg, regardless of its timing, enhances the colon cleansing action of PEG-ELS in guinea pigs. On the other hand, in the guinea pigs treated with mosapride (10 mg/kg), only the regimen given twice (at the start and at the end of PEG-ELS administration) significantly reduced both weights of colonic content (Fig. 6). The present results suggest that this

regimen may be effective in reducing fecal residue and excessive fluid in the colonic lumen. One explanation for the beneficial effect of mosapride at the end of PEG-ELS administration is that mosapride does not last throughout PEG-ELS administration due to its short half-life (24). In addition, our data show that mosapride (5 mg/kg) given twice (at the start and at the end of PEG-ELS administration) is more effective than mosapride (10 mg/kg) given at the end of PEG-ELS administration in reducing the weight of water colonic content. This result may suggest that the AUC (area under the plasma concentration vs. time curve) of mosapride given twice (at the start and at the end of PEG-ELS) is higher than that of mosapride given at the end of PEG-ELS. However, further pharmacokinetic studies are needed to explain these results.

In a recent clinical study using a barium enema preparation in which 20 mg of mosapride was given at the start of PEG-ELS administration and 20 mg mosapride was also given at the end of PEG-ELS administration, noninferiority to the modified Brown's method was confirmed (25). Our data using guinea pigs supports the utility of this clinical preparation method where mosapride is given twice (at the start and at the end of PEG-ELS administration).

In addition, we examined the effect of metoclopramide, another gastroprokinetic drug, on the colon cleansing action of PEG-ELS and compared it with the effect of mosapride (Fig. 7). We found that metoclopramide (50 mg/kg) enhanced the colon cleansing action of PEG-ELS as well as mosapride (20 mg/kg). It is well known that metoclopramide has 5-HT₄-receptor agonist and 5-HT₃-receptor antagonist activities as well as dopamine D₂-receptor antagonist activity. In addition, *in vitro* studies indicated that colonic contraction induced by metoclopramide in guinea pigs is mainly involved in stimulation of 5-HT₄ receptors (26). From these findings, it is suggested that the enhancing effect of metoclopramide, as well as mosapride, on the colon cleansing action of PEG-ELS is due to accelerated colonic motility by stimulating 5-HT₄ receptors. On the other hand, the blockage of the dopamine D₂-receptor by metoclopramide is known to induce extrapyramidal syndrome and hyperprolactinaemia in humans, giving a limitation in clinical use (27). From the clinical point of view, mosapride, unlike metoclopramide, is useful for colon preparation for barium enema examination.

In conclusion, we have shown in this study that mosapride enhances the colon cleansing action of PEG-ELS in guinea pigs and that this enhancement is via increase in colonic transit. These findings indicate that coadministration of mosapride and PEG-ELS according to an appropriate regimen may allow better visualization

in barium enema examination because mosapride reduces the amount of lavage solution in the colon. In addition, mosapride, unlike cisapride or metoclopramide, has no troublesome side effects that influence the central nervous system or the cardiovascular system.

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