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The Effects of Prucalopride on Postoperative Ileus in Guinea Pigs

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Purpose: Postoperative ileus (POI) is an impairment of coordinated gastrointestinal (GI) motility that develops as a consequence of abdominal surgery and is a major factor contributing to patient morbidity and prolonged hospitalization. The aim of this study was to investigate the effects of different 5-hydroxytryptamine 4 (5-HT_4) receptor agonists, which stimulate excitatory pathways, on a POI model. **Materials and Methods:** The experimental model of POI in guinea pigs was created by laparotomy, gentle manipulation of the cecum for 60 seconds, and closure by suture, all under anesthesia. Different degrees of restoration of GI transit were measured by the migration of charcoal. Colonic transit was indirectly assessed via measurement of fecal pellet output every hour for 5 hours after administration of various doses of mosapride, tegaserod, prucalopride, and 5-HT. **Results:** Charcoal transit assay showed that various 5-HT_4 receptor agonists can accelerate delayed upper GI transit in a dose-dependent manner. However, fecal pellet output assay suggested that only prucalopride had a significant effect in accelerating colonic motility in POI. **Conclusion:** Although mosapride, tegaserod, and prucalopride produce beneficial effects to hasten upper GI transit in the POI model, prucalopride administered orally restores lower GI transit as well as upper GI transit after operation in a conscious guinea pig. This drug may serve as a useful candidate for examination in a clinical trial for POI.

Key Words: Postoperative ileus, 5-HT_4 receptor agonist, gastrointestinal transit, prucalopride

INTRODUCTION

Postoperative ileus (POI) is the transient impairment of gastrointestinal (GI) motility that develops as a consequence of almost every abdominal surgical procedure and usually lasts 2-4 days for a conventional abdominal procedure but decreases to as little as ≤2 days in the case of laparoscopic surgery.[1] Uncomplicated POI is generally recognized as a physiological response of the intestine to a traumatic event and thus can be disregarded. However, if POI is prolonged and left untreated, it may require nasogastric intubation and sometimes even parenteral nutrition. In addition, evidence continues to accumulate indicating that POI is accompanied by a significant increase in patient morbidity and by substantial hospitalization costs. A drug that could prevent or treat POI and shorten a patient's hospital stay may lead

to a significant reduction in healthcare costs and, more importantly, will allow patients to leave the hospital earlier, lessen the possibility of acquiring serious hospital-based infections, and promote faster recovery from abdominal surgery.[2]

It has been reported that impairment of GI motility induced by surgery is a result of multiple causes, including neural, inflammatory, and pharmacological mechanisms.[3] Of these mechanisms, it is the neural pathways that are mainly activated in the acute postoperative phase. Neural pathways are complicated, and are influenced by the number of factors including intensity of the stimulus. Briefly, incision of the skin and laparotomy activate the adrenergic inhibitory pathway, while gastrointestinal surgery involving handling of the bowel stimulates supra-spinal pathways that activate the hypothalamic-pituitary-adrenal stress axis and release corticotrophin-releasing factor. Moreover, GI motility may be inhibited by non-adrenergic, non-cholinergic (NANC) pathways. Multiple inhibitory NANC neurotransmitters (e.g. nitric oxide, calcitonin gene-related peptide, vasoactive intestinal polypeptide) located in the enteric nervous systems may also play an important role in the pathogenesis of POI.[2,4] Herein, the authors hypothesized that stimulation of excitatory pathways could overcome the inhibitory neural pathways and ultimately prevent or improve POI.

The 5-hydroxytryptamine 4 (5-HT_4) receptor is an important drug target for medications intended to stimulate GI motility. Medications that act as agonists at this receptor have been shown to have therapeutic potential in the treatment of GI motility disorders. Unfortunately, older 5-HT_4 receptor agonists were less selective and less specific, which caused them to have potential adverse cardiac effects or reduced intestinal prokinetic activity due to interactions with other 5-HT receptors (e.g., antagonism at the 5-HT_3 receptor, as seen with cisapride). Additionally, the prokinetic agents which have effects mainly in the upper GI tract have not been proven effective in treating POI, likely because of their limited efficacy and inability to reverse the delay in large bowel transit following abdominal surgery. Despite the development of newer 5-HT_4 receptor agonists, only limited data comparing the efficacies of the newer drugs to those of the previously existing 5-HT_4 receptor agonists has been reported. Herein, we evaluated the effects of 5-HT and various 5-HT_4 receptor agonists including mosapride, tegaserod, and prucalopride on a guinea pig model of POI.

MATERIALS AND METHODS

Preparation of animals

Adult male Hartley guinea pigs (250-350 g, Charles River Laboratories, Inc., Wilmington, MA, USA) were acclimated to their holding room (temperature controlled at 21±1°C, 50±10% humidity, and 12 h light/dark cycle commencing at 7:00 AM) for at least 1 week prior to surgery. A standard guinea pig diet and drinking water were provided ad libitum. All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals provided by the Animal Laboratory Ethics Committees of the Department of Laboratory Animal Medicine, Medical Research Center, Yonsei University College of Medicine.

Experimental design

Guinea pigs were subjected to a 24-hour fast with free access to water before being anesthetized by intraperitoneal injection with pentobarbital sodium. The guinea pigs were randomly divided into three groups. In the first group, no incision or laparotomy was made under anesthesia ('anesthesia' group). The second group had a laparotomy that consisted of an incision through the abdominal skin, abdominal muscle layers, and peritoneum and closure by suture after the abdomen had been shaved and disinfected with 70% alcohol ('sham operation' group). The third group had a laparotomy followed by evisceration and gentle manipulation of the cecum using wet gauze for 60 seconds and was then closed by suture ('POI' group). After the group-specific treatments, guinea pigs received vehicle, mosapride, tegaserod, prucalopride, or 5-HT through an orogastric cannula. All experiments were performed in the morning between 8:00 AM and noon.

Experimental design 1: upper GI transit

In the first series of experiments, the effects of various prokinetic agents were tested via charcoal transit assay. The charcoal mixture consisted of charcoal, barium, and normal saline mixed in the ratio of 1 : 2 : 6. After the operations, the guinea pigs received an intragastric administration of charcoal mixture combined with vehicle (0.9% normal saline, 1, 5, 10 mg kg^{-1}, p.o.), mosapride (1, 5, 10 mg kg^{-1}, p.o.), tegaserod (1, 5, 10 mg kg^{-1}, p.o.), prucalopride (0.5, 1, 5, 10 mg kg^{-1}, p.o.), or 5-HT (1, 5, 10 mg kg^{-1}, p.o.) through an orogastric cannula. Doses were selected based upon the results of our preliminary experiments as well as published

data.[5] After 3 hours, the guinea pigs were sacrificed in the CO_2 room. Upper GI transit was evaluated using the migration of charcoal mixture from the pylorus to the most distal point of migration, and charcoal migration was expressed as a percentage (%) of the total length of the small intestine (cm). The upper GI transit experiment was performed 3 hours after surgery, based on the results of our preliminary experiments based on simple abdominal X-rays (Fig. 1).

Experimental design 2: lower GI transit

In the second series of experiments, we tested the effects of various prokinetic agents using a fecal pellet output assay. We did not perform the fecal pellet output assay with the 'sham operation' group because there was no difference in upper GI transit between the 'sham operation' and 'anesthesia' groups in our preliminary data. Fecal pellet output was measured in non-fasted guinea pigs receiving an intragastric administration of vehicle (0.9% normal saline, 1, 5, 10 mg kg^{-1}, p.o.), mosapride (1, 5, 10 mg kg^{-1}, p.o.), tegaserod (1, 5, 10 mg kg^{-1}, p.o.), prucalopride (0.5, 1, 5, 10 mg kg^{-1}, p.o.), or 5-HT (1, 5, 10 mg kg^{-1}, p.o.) through an orogastric cannula 1.5 hours after the anesthesia with or without operation. Each guinea pig was placed into an individual experimental cage, and both weight and number of fecal pellets produced were measured and recorded in 1-hour increments for the first 4 hours and in 30-minute increments for the last 1 hour. As a result, a 5-hour cumulative fecal pellet output was measured for each guinea pig.

Drugs and chemicals

The following drugs and chemicals were used: pentobarbital sodium (Hanlim Pharmaceuticals, Gyeonggi-do, Korea), isotonic sodium chloride solution (Dai Han Pharmaceuticals, Seoul, Korea), charcoal (Sigma, Milwaukee, WI, USA), barium sulfate (Tae Joon Pharmaceuticals, Seoul, Korea), mosapride (Dainippon Pharmaceuticals, Osaka, Japan), tegaserod maleate (Toronto Research Chemicals, North York, Canada), prucalopride (Janssen Pharmaceuticals, Beerse, Belgium), and 5-HT (Sigma, Buchs, Switzerland, EU). These chemicals were freshly made for each experiment by dissolving each compound in isotonic sodium chloride solution.

Data analysis

The results of the upper GI transit experiment described the distance migrated by charcoal (cm) as a percentage (%) of the total length of the small intestine (cm). The measurements of charcoal migration were made from the pylorus to the most distal point of migration of charcoal mixture, and the total length of the small intestine was evaluated from the pylorus to the end of the ileum at the time point 3 hours after administration of vehicle or drug. The results of the lower GI transit experiment are reported as the cumulative fecal pellet output including weight (g) and number at each of time point during the 5 hours after administration of vehicle or drug. For the charcoal transit assay, statistical significance was evaluated among the 'anesthesia', 'sham operation', and 'POI' groups using one-way ANOVA followed by a post-hoc Bonferroni test. For charcoal transit and fecal pellet output assays in the 'POI' group, statistical significance was assessed between the vehicle and each drug treatment by two-way ANOVA followed by the post-hoc Bonferroni test. To determine if the effects of drug treatment alone on charcoal transit and fecal pellet output were dose-dependent, 'within group' comparisons were made for the various doses at the same time-point using one-way ANOVA and the post-hoc Bonferroni test. In all tests, statistical significance was assigned at $p<0.05$, based on the means from collected data. All data were analyzed using SPSS version 18.0 for Windows software (SPSS Inc., Chicago, IL, USA).

RESULTS

Upper and lower GI transits in the POI model

The migration length of charcoal as a percentage (%) of the

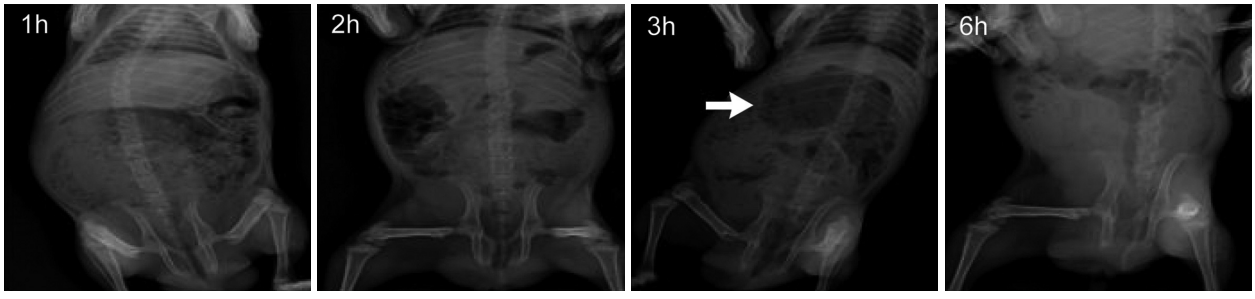

Fig. 1. Radiologic images of postoperative ileus in a guinea pig model. The level of gas distention peaked at 3 hours after the operation (arrow).

total small intestine length (cm) was 68.7±29.4% (n=7) and 66.3±24.4% (n=5) in the 'anesthesia' and 'sham operation' groups, respectively (p>0.999). In the POI group, however, the charcoal migration length was 0.7±1.3% (n=7), which equates to almost no charcoal mixture moving into the small intestine. This difference was significant after post-hoc analysis of the upper GI transit results among the 'POI' group, 'anesthesia' group, and 'sham operation' group (0.7% vs. 68.7% vs. 66.3%, p<0.001) (Fig. 2).

The cumulative weights (g) of fecal pellets were significantly different at all time points from 2 h to 5 h between the 'anesthesia' and 'POI' groups (2.2 g vs. 0 g at 2 h, p=0.002; 2.4 g vs. 0 g at 3 h, p=0.008; 2.8 g vs. 0 g at 4 h, p=0.002; 3.0 g vs. 0.2 g at 4.5 h, p=0.003; 3.4 g vs. 0.5 g at 5 h, p=0.009). However, there was no significant difference in cumulative fecal pellet weight (g) between the 'anesthesia' and 'POI' groups at 1 h (1.3 g vs. 0 g at 1 h, p=0.075) (Fig. 3A). As shown in Fig. 3B, the cumulative numbers of fecal pellets showed significant differences between the 'anesthesia' and 'POI' groups at all time-points from 1 h to 5 h. In short, upper GI motility was significantly delayed in the 'POI' group compared to both the 'anesthesia' and 'sham operation' groups, and lower GI motility was also significantly hampered in the 'POI' group compared to the 'anesthesia' group.

Effects of 5-HT$_4$ agonists on upper GI transit

The first series of dose-response experiments used the charcoal transit assay to investigate upper GI transit after stimulation by various doses of mosapride, tegaserod, prucalopride, or 5-HT. Following all drug treatments, upper GI transit was restored in a dose-dependent manner, increasing the ratio of charcoal migration to the total length of small intestine (Fig. 2).

The percentage of charcoal transit after administration of the highest dose (10 mg kg^{-1}: n=8, 64.1±29.6%) of mosapride was significantly increased compared to rates of transit after administration of vehicle (POI group: n=7, 0.7 ±1.3%, p<0.001) or the lowest dose of mosapride (1 mg kg^{-1}: n=7, 12.4±11.1%, p<0.001) after Bonferroni analysis. The percentage of charcoal transit after administration of the highest dose of tegaserod (10 mg kg^{-1}: n=5, 85.6±12.8%) was significantly higher than those after administration of vehicle (POI group: p<0.001) and the lowest dose of tegaserod (1 mg kg^{-1}: n=5, 17.2±23.7%, p<0.001) after Bonferroni analysis. The percentage of charcoal transit after administration of the highest dose of prucalopride (10 mg kg^{-1}: n=5, 83.5±11.3%) was significantly increased compared to those following administration of vehicle in the 'POI' group (p<0.001) and the lowest dose of prucalopride (0.5 mg kg^{-1}: n=5, 2.7±3.2%, p<0.001) after Bonferroni analysis. The results of the charcoal transit assay in the prucalopride groups treated with 1 mg kg^{-1} (n=4, 67.7±18.7%, p<0.001) or 5 mg kg^{-1} (n=5, 78.9±20.7%, p<0.001) also showed significant differences compared with the vehicle-treated POI group.

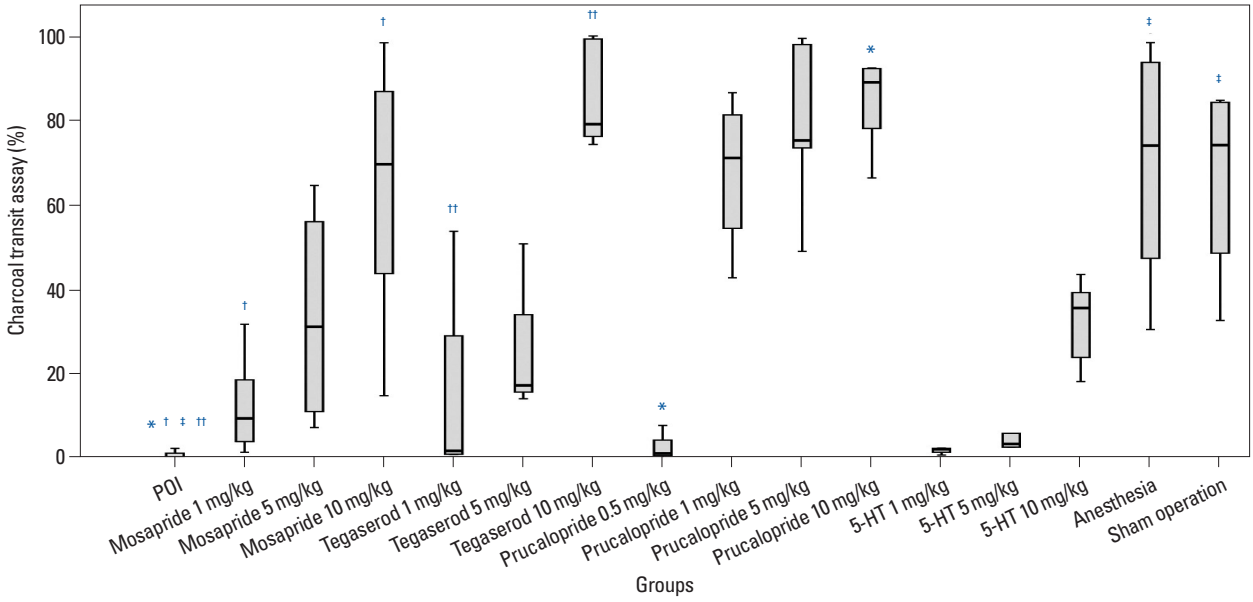

Fig. 2. Results of the charcoal transit assay with various doses of mosapride, tegaserod, prucalopride, and 5-HT compared to postoperative ileus (POI), anesthesia, and sham operation groups. *Significant p value in prucalopride (10 mg/kg) group compared to POI and prucalopride (0.5 mg/kg) groups after Bonferroni analysis. †Significant p value in mosapride (10 mg/kg) group compared to POI and mosapride (1 mg/kg) groups after Bonferroni analysis. ‡Significant p value in anethesia and sham operation groups compared with POI group after Bonferroni analysis. ††Significant p value in tegasored (10 mg/kg) group compared to POI and tegaserod (1 mg/kg) groups after Bonferroni analysis. 5-HT, 5-hydroxytryptamine.

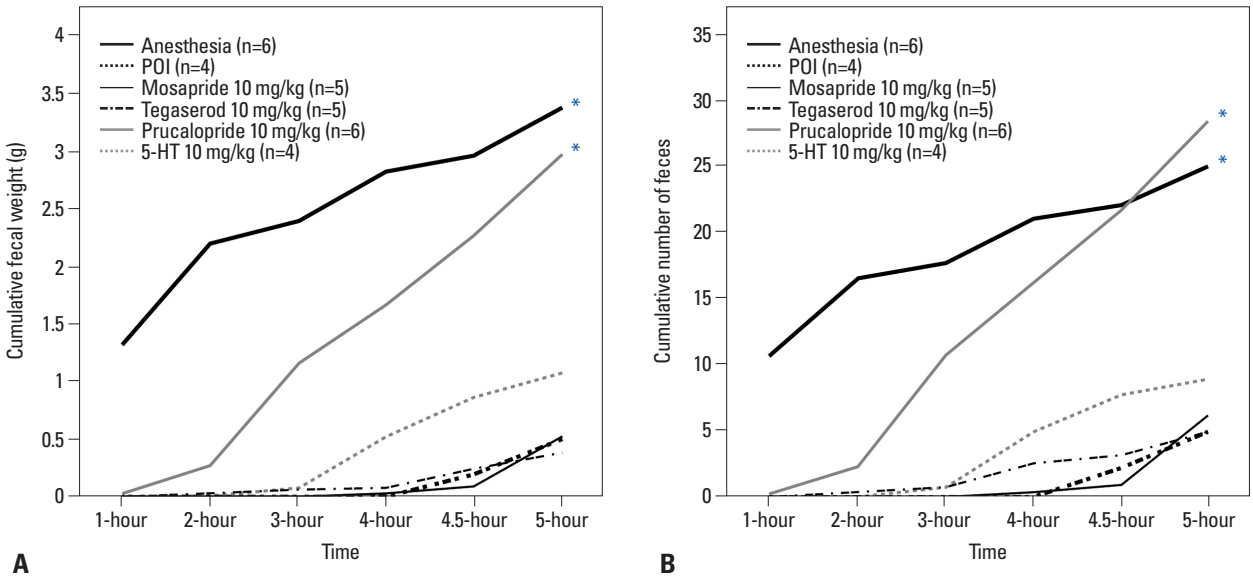

Fig. 3. Results of fecal expulsion assay with the maximal doses (10 mg/kg^{-1}) of each drug. (A) Cumulative fecal weights (g). (B) Cumulative numbers of fecal pellets. *Significant *p* value compared with POI group. POI, postoperative ileus; 5-HT, 5-hydroxytryptamine.

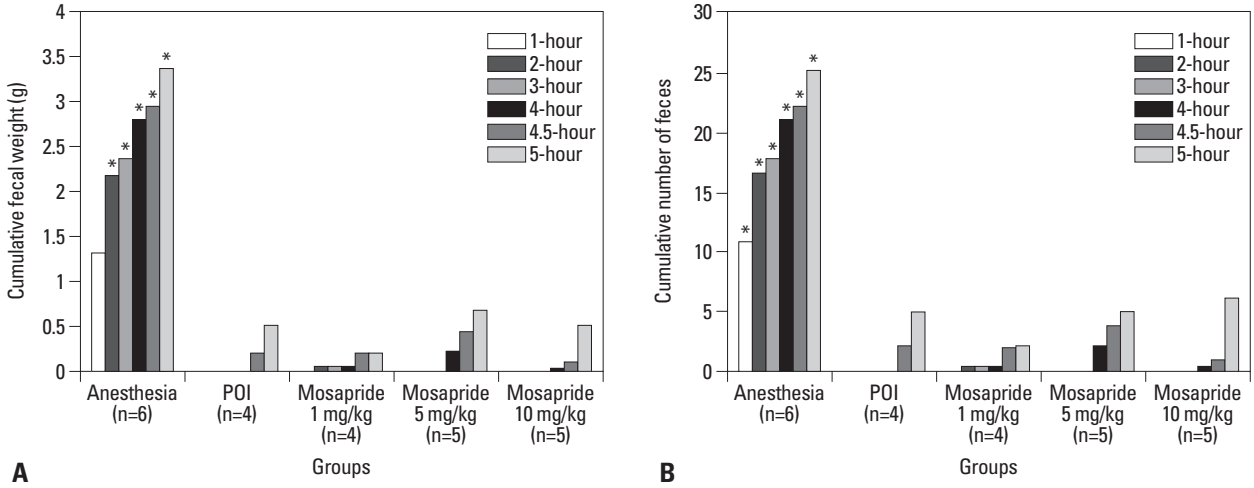

Fig. 4. The effects of mosapride on increasing cumulative fecal weight (g) and pellet number at each time-point, compared to the 'anestheia' and 'POI' groups. (A) Cumulative fecal weights (g). (B) Cumulative numbers of fecal pellets. *Significant *p* value compared with the same time-point in the 'POI' group. POI, postoperative ileus.

In contrast, the results of charcoal transit after administration of various doses of 5-HT (1 mg kg^{-1}: n=4, 1.8±0.8%, p>0.999; 5 mg kg^{-1}: n=5, 6.2±5.9%, p>0.999; 10 mg kg^{-1}: n=5, 32.0±10.7%, p=0.606) were not significantly different compared to those after administration of vehicle. At the highest doses tested, tegaserod and prucalopride achieved similar maximum prokinetic effects (equivalent to approximately 83-85% increases in charcoal transit).

Interestingly, 1 mg kg^{-1} of prucalopride was as potent as 10 mg kg^{-1} of mosapride or tegaserod by one-way ANOVA and Bonferroni test (p>0.999). Prucalopride, furthermore, showed considerable restoration of charcoal transit (67.7% at a dosage of 1 mg kg^{-1}), a result equivalent to the 68.7% of that of the 'anesthesia' group and 66.3% of that of the 'sham operation' group.

Effects of 5-HT$_4$ agonists on lower GI transit

The second series of experiments was carried out to examine fecal pellet output after treatment with various doses of mosapride, tegaserod, prucalopride, or 5-HT. In vehicle-treated (10 mg kg^{-1}) guinea pigs of the POI group, the mean cumulative amount of excreted fecal pellets for 5 hours was 0.5 g (n=6) (Fig. 3A). Following treatment with the highest dose (10 mg kg^{-1}) of mosapride, tegaserod, or 5-HT, there was no significant increase in fecal pellet output (0.5 g, 0.4 g, and 1.0 g, p>0.999 for all) compared to the vehicle-treated 'POI' group (0.5 g) (Figs. 4A, 5A, and 6A). Following treatment with prucalopride, however, delayed colonic mo-

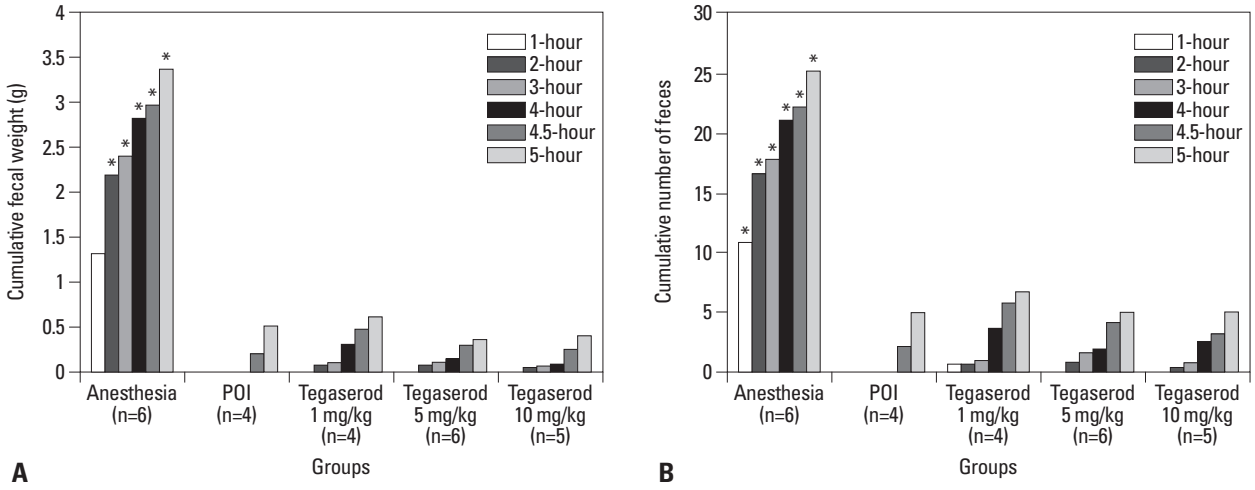

Fig. 5. The effects of tegaserod on increasing cumulative fecal weight (g) and pellet number at each time-point, compared to the 'anestheia' and 'POI' groups. (A) Cumulative fecal weights (g). (B) Cumulative numbers of fecal pellets. *Significant *p* value compared with the same time-point in the 'POI' group. POI, postoperative ileus.

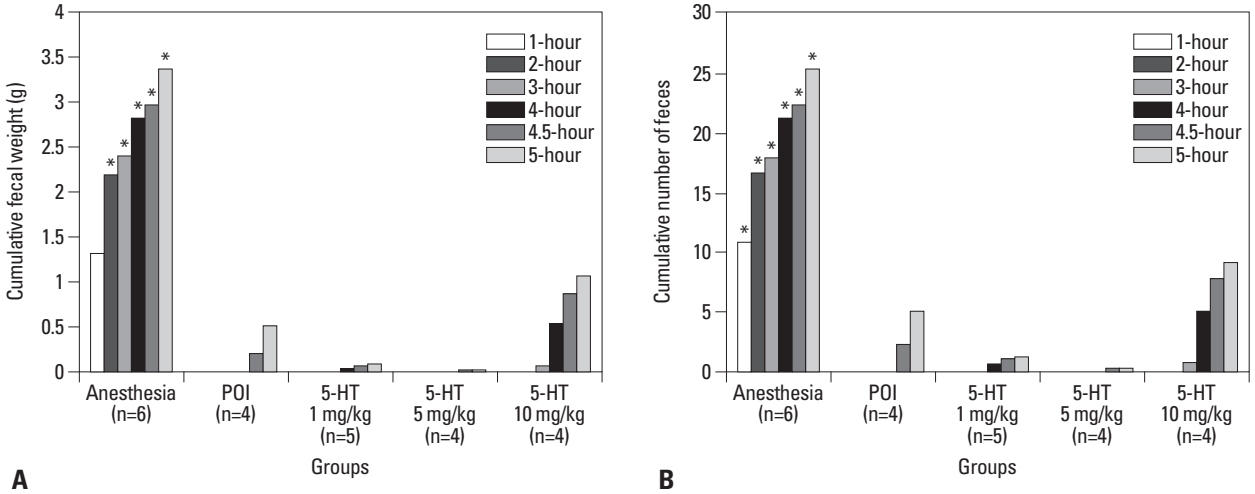

Fig. 6. The effects of 5-HT on increasing cumulative fecal weight (g) and pellet number at each time-point, compared to the 'anestheia' and 'POI' groups. (A) Cumulative fecal weights (g). (B) Cumulative numbers of fecal pellets. *Significant *p* value compared with the same time-point in the 'POI' group. POI, postoperative ileus; 5-HT, 5-hydroxytryptamine.

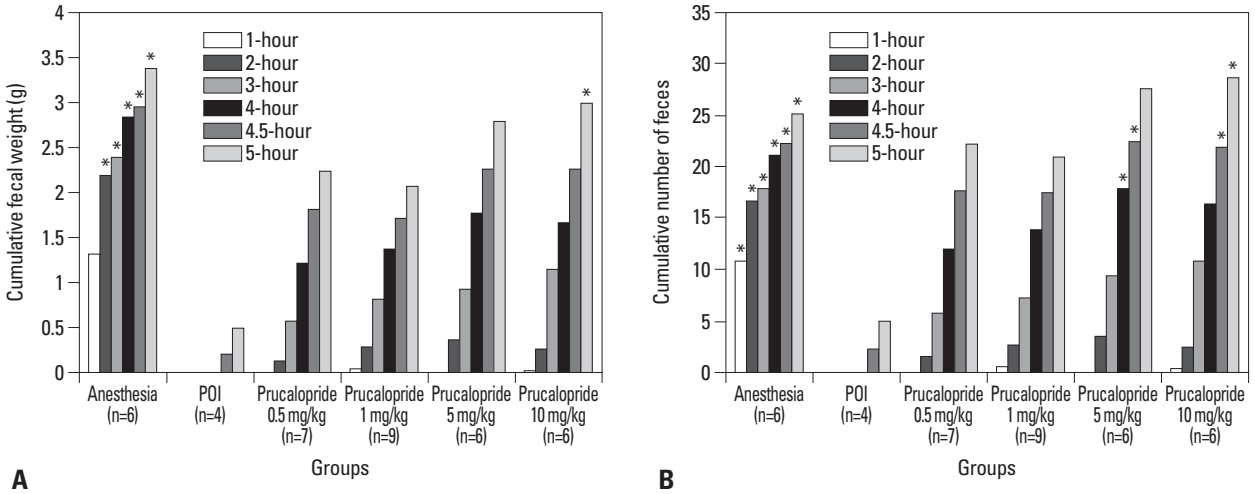

Fig. 7. The effects of prucalopride on increasing cumulative fecal weight (g) and pellet number at each time-point, compared to the 'anestheia' and 'POI' groups. (A) Cumulative fecal weights (g). (B) Cumulative numbers of fecal pellets. *Significant *p* value compared with the same time-point in the 'POI' group. POI, postoperative ileus.

tility was reversed, resulting in an increase in excreted fecal weight compared to the vehicle-treated 'POI' group (3.0 g vs. 0.5 g, p=0.035) (Fig. 7A). In prucalopride-treated guinea pigs, the mean cumulative amount of excreted fecal pellets for the 5 hours following treatment were 2.2 g at the dose of 0.5 mg kg^{-1}, 2.1 g at 1 mg kg^{-1}, 2.8 g at 5 mg kg^{-1}, and 3.0 g at 10 mg kg^{-1}. Only prucalopride significantly increased the amount of fecal pellet expelled (g) at the dose of 10 mg kg^{-1} (3.0 g vs. 0.5 g, p=0.035). There were no statistically significant differences in the doses of prucalopride lower than 10 mg kg^{-1}.

The average cumulative number of fecal pellets expelled during the 5 hours after treatment was 25.2 in the 'anesthesia' group (n=6). In contrast, in the vehicle-treated (10 mg kg^{-1}) 'POI' guinea pigs, the average number of pellets was 5.0 (n=4). In the groups treated with the highest doses of mosapride, tegaserod, or 5-HT (10 mg kg^{-1}), the average numbers of pellets generated were 6.2 (n=5), 5.0 (n=5), and 9.0 (n=4), respectively (Figs. 4B, 5B, and 6B). None of these values were significantly different from that of the vehicle-treated 'POI' guinea pigs, and no significant changes in pellet expulsion were found with any of the lower concentrations of these drugs. Furthermore, there were no statistically significant increments in the number of fecal expulsion in any doses of mosapride, tegaserod, or 5-HT, except for prucalopride at 4 h (17.8 vs. 0, p=0.026) and 4.5 h (22.3 vs. 2.25, p=0.050) at a dose of 5 mg kg^{-1} compared to the vehicle-treated 'POI' group, respectively, and at 4.5 h (21.8 vs. 2.25, p=0.001) and 5 h (28.7 vs. 5.0, p=0.005) at the dose of 10 mg kg^{-1} compared to the vehicle-treated 'POI' group, respectively (Fig. 7B). Overall, only prucalopride significantly increased fecal pellet weight and number in our experiments.

DISCUSSION

In this study, we demonstrated that oral administration of 5-HT$_4$ receptor agonists (mosapride, tegaserod, and prucalopride) and 5-HT restored the delayed upper GI transit in a dose-dependent manner in a POI model, as determined by charcoal transit assay. However, only prucalopride clearly reversed the impeded colonic motility in the POI model, based on fecal pellet output.

Our *in vivo* data on 5-HT$_4$ receptor-mediated stimulation of colonic motility with prucalopride was in agreement with published *in vitro* data on guinea pig[6,7] and *in vivo* data on dog[8] and rat.[9] In contrast to these published data, one previous study in a 'POI' animal model showed that prucalopride only tended to increase colonic motility, and its effect was not clearly dose related. Only the lower dose (1 mg kg^{-1}) of the drug significantly increased transit in the 'sham operation' group but not in the 'POI' group.[5] This data is different from our results showing that prucalopride is the most effective 5-HT$_4$ agonist to accelerate GI transit and increases both the weight and number of fecal pellets at the maximal dose (10 mg kg^{-1}) in the 'POI' group. This discrepancy may be explained by the differences in the methods used and species employed in the POI model. In the contradicting study, prucalopride was injected intravenously into fasted rats 1 minute before the operation, and they were sacrificed 20 minutes after intragastric administration of 0.1 mL Evans blue.[5] Intestinal transit was measured as the migration of Evans blue from the pylorus to the most distal point of migration. Our methods are applicable to a clinical situation because the experiments were performed at the time of the worst stage of POI in guinea pig (3 hours after operation) and various 5-HT$_4$ receptor agonists are commercially available as oral drugs. Although the opposing study used a different species, the 20-minute time point used may have been too early to compare the effects of the drugs. Furthermore, our fecal expulsion assay may be a more physiologic test for the comparison of the recovery of hampered colonic motility.

As POI represents a clinical indication for which there have been few approved therapies worldwide, vigorous studies are in progress to develop new drugs that inhibit neuroinflammatory or pharmacologic mechanisms. In POI, a local inflammatory process triggered by handling of the intestine activates inhibitory neural pathways and possibly triggers inflammation at distant untouched areas, leading to a generalized impairment of gastrointestinal motility.[4] Thus, the use of prokinetic therapy to overcome an inhibitory neural pathway may lessen the severity of POI; however, the therapeutic efficacies of agents that stimulate propulsive patterns of GI motility have been disappointing. Although the reason for the lack of efficacy of prokinetics for the treatment of POI is unknown, it may relate to the fact that, in clinical trials, the compounds that have been studied have greater effects in promoting upper GI transit rather than stimulating colonic transit. That is, if a drug has effects on the stomach and the small intestine but not on the colon, such a drug would not be a successful treatment for POI in the clinic. Thus, the strategy for development of novel thera-

peutics to prevent and treat POI requires the use of preclinical models of POI to investigate newer prokinetics that have already been shown to have marked effects to promote transit throughout the GI tract, especially in the colon.

Prucalopride is a highly selective, high-affinity 5-HT_4 receptor agonist that exerts an enterokinetic effect by binding with 5-HT_4 receptors on enteric neurons and facilitates cholinergic and non-adrenergic, non-cholinergic neurotransmission. It is one of the most advanced 5-HT_4 receptor agonists in clinical development. The safety and long-term efficacy of the use of prucalopride have been evaluated in its use as treatment for chronic constipation, opioid-induced constipation, and chronic intestinal pseudoobstruction in several pivotal clinical trials.[10-15] Prucalopride was approved in Europe in 2009 and in Canada in 2011 for the symptomatic treatment of chronic constipation in women for whom laxatives (medicines that trigger bowel movements) do not work well enough. Furthermore, assessment of the cardiac safety of prucalopride was reported in healthy volunteers.[16] Therefore, further research to explore the potential beneficial effects of prucalopride in other disease entities such as POI is worthwhile.

5-HT_4 receptors are present in all segments of the human GI tract and are expressed on enterochromaffin cells, intrinsic primary afferent neurons, interneurons and efferent neurons of the myenteric plexus, and smooth muscle cells. The activation of these receptors can thereby facilitate the peristaltic reflex and accelerate GI transit.[17,18] It is not known why the effects of the various 5-HT_4 receptor agonists would differ between upper and lower GI transit in our experiments, but it could be partly explained by the selectivity of 5-HT_4 receptor agonists. The selectivity issue for receptors is not only an important determinant of the benefit/risk profile, but is also an influencing factor in efficacy. For example, tegaserod, in addition to its affinity for 5-HT_4 receptors, has antagonistic affinity for 5-HT_{2A} and 5-HT_{2B} receptors. In terms of efficacy, it is possible that the antagonistic properties of this drug at 5-$HT_{2A/2B}$ receptors negatively influence the drug's prokinetic activity. Similarly, mosapride also antagonizes the 5-HT_3 receptor that reduces intestinal contractility, slows colonic transit, and increases fluid absorption. These properties may explain why mosapride exerts potent prokinetic effects in the upper GI tract but has less clear effects on colonic motility both *in vitro* and *in vivo*.[8,19-21]

In addition to the discovery of selective agonists such as prucalopride, the issues of 5-HT_4 receptor-related differences between agonists have come into the spotlight. Based on tissue-related properties (e.g., differences in receptor binding, agonist-specific signal transduction pathways, receptor density, coupling efficiency influenced by splice variants, and receptor desensitization), 5-HT_4 receptor agonists are able to express tissue selectivity.[17] Although the complexity and incompleteness of the underlying mechanisms hinder a clear-cut interpretation, some data on tissue-specificity has been published. Prucalopride stimulates 5-HT_4 receptors on canine colon, which affects a regional coordinated relaxation-contraction mechanism *in vivo*.[8] It induces to increase the motility pattern in the proximal colon and decrease the pattern motility in the distal colon. As a result, it facilitates the propulsion of luminal contents. This finding was similar to our previous results regarding mosapride.[22] In addition, prucalopride apparently provokes propulsive waves of contractions, named colonic giant migrating contractions, starting in the proximal colon and progressing all the way to the anus.[8] In contrast, tegaserod does not induce giant migrating contractions in the canine colon.[20] Further studies are warranted to identify the mechanism of prucalopride to increase colonic transit.

In conclusion, the newer 5-HT_4 receptor agonist, prucalopride, has clear-cut beneficial effects in the POI guinea pig model. Although mosapride and tegaserod also showed beneficial effects for the treatment of delayed upper GI transit, they may be of limited use in the treatment of POI. Prucalopride administered orally restores lower GI transit as well as upper GI transit after operation in a conscious guinea pig. This drug may serve as a useful candidate for examination in a clinical trial for POI.

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