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Laxative and Anti-diarrheal Activity of Polycarbophil in Mice and Rats

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ABSTRACT—We investigated the laxative and anti-diarrheal activity of polycarbophil, an insoluble hydrophilic polymer, in comparison with other agents used for treating functional bowel disorder (FBD). In naive rats, polycarbophil (500 mg/kg) increased fecal weight and water contents without producing diarrhea. Carboxymethylcellulose (CMC) did not produce evident changes in bowel movement. Picosulfate markedly produced diarrhea. Loperamide, trimebutine and granisetron decreased stool output dose-dependently. Constipation, indicated by decrease in fecal weight, was produced by loperamide and clonidine in rats. Polycarbophil (500 mg/kg) and CMC increased fecal weight without diarrhea. Conversely trimebutine further decreased fecal weight in constipated rats. Polycarbophil (500 mg/kg) suppressed diarrhea induced by castor oil, and at 250 – 500 mg/kg, it produced shaped stools in animals with stools loosened by prostaglandin E_2, serotonin or carbachol in mice. Polycarbophil (500 mg/kg) also reduced stools in rats with stool output increased by wrap restraint stress (WRS). CMC had no effect in the diarrhea models, except for carbachol-induced diarrhea, and WRS-induced evacuation. Loperamide, trimebutine and granisetron inhibited diarrhea production and WRS-induced evacuation, except for carbachol-induced diarrhea. The results show that polycarbophil prevents constipation and diarrhea without inducing diarrhea or constipation, which is different from the other agents. Hydrophilic polymers such as polycarbophil will be promising agents for the treatment of FBD.

Keywords: Polycarbophil, Hydrophilic polymer, Bowel movement, Functional bowel disorder, Irritable bowel syndrome

Constipation and/or diarrhea, while not life-threatening, have caused much discomfort affecting the quality of life. Recently, functional bowel disorder (FBD) has been defined as a disorder with symptoms attributable to the mid or lower gastrointestinal tract, including functional constipation, functional diarrhea and irritable bowel syndrome (IBS), although the precise etiologic basis of FBD is not known (1). FBD is diagnosed by characteristic symptoms in the absence of a structural or biochemical explanation; and with respect to IBS, the most common symptoms are abdominal pain or discomfort associated with alternating constipation and diarrhea (1, 2). It is assumed that IBS is a complex disorder with physiologic and psychosocial components in which altered motility or sensation in the intestine is modulated by input from the central nervous system (3). The treatments most commonly recommended for FBD are dietary fiber/bulking agents, stimulant laxatives, prokinetics, opiates, anticholinergic/antispasmodic agents, and sometimes antidepressants depending on the dominant symptoms, their severity, and any psychosocial factors (1). The efficacy of other types of opiates (4) and 5-HT_3-receptor antagonists (5) on the reduction of visceral hypersensitivity are promising and the clinical development of new drugs with other modes of action is in progress.

Polycarbophil, a high-molecular hydrophilic polymer, is polyacrylic acid cross-linked with divinyl glycol (6). Polycarbophil is insoluble and has the ability under neutral conditions, but not under acidic conditions, to absorb around 70 times its original weight of water, and so swelling (7). Although the clinical usefulness of hydrophilic agents for constipation and/or diarrhea has been reported (8 – 10), there are few reliable reports obtained from well-controlled and detailed studies. Even in experimental animals, the laxative and anti-diarrheal activities of bulking agents, including polycarbophil compounds, have not yet been clarified. Thus the effectiveness of the water holding and swelling (gelling) properties observed in in vitro experiments, in vivo experiments and FBD patients is not known. Reliable data on the value of hydrophilic compounds in treating constipation and diarrhea in experimental animals

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may help to evaluate the effectiveness of the new drugs for the treatment of FBD. In the present study, we investigated the laxative and anti-diarrheal activity of polycarbophil, a typical insoluble hydrophilic agent, in comparison with carboxymethylcellulose (CMC), a soluble agent, and other conventional agents used for treating FBD.

MATERIALS AND METHODS

Animals

Male Wistar rats, CD-1 (ICR) mice (Charles River Japan, Inc., Hino) or Sprague-Dawley (SD) rats (Clea Japan Inc., Tokyo) were used. The animals were housed under standard conditions at a room temperature of 20 – 26°C and humidity of 30 – 70% with a 12-h light-dark cycle (light on at 7:00 AM). They were given solid food for laboratory animals (Oriental Yeast Co., Ltd., Tokyo), providing adequate nutrition (360 kcal/100 g including crude protein: 24.6%, crude fat: 5.6%, dry matter: 6.3%, crude fiber: 3.1%, and nitrogen-free extract: 52.8%) and water ad libitum. The animals were allowed to acclimate to the environment for at least 7 days and were then put into individual cages before initiating the study. For studying inhibitory effects on diarrhea, the animals were fasted overnight but allowed free access to water before the experiments, but water was removed after dosing. The other experiments including wrap resistance stress (WRS)-defecation were performed in non-fasted animals; however, the animals were deprived of food and water after drug administration in order to avoid any effect of food intake on the quantity of feces produced. The animal experiments in this study were conducted in accordance with guidelines issued by the Hokuriku Seiyaku Co., Ltd., Animal Care and Use Committee.

Fecal output in naive rats

SD rats weighing 238 – 332 g were used. The consistency of the stools expelled within 24 h after the administration of each drug or vehicle was investigated. When the feces became unformed, i.e., muddy or watery, this was judged to be diarrhea and the percentage diarrhea was reported as the ratio of the number of animals producing unformed stools to the number tested. All of the feces were collected just after each evacuation and put into a covered vessel prepared for each animal in order to prevent the feces from drying. To investigate the duration of activity of each drug, the feces collected over each 8-h period were dried for more than 8 h at 70°C in a ventilated oven after the wet weight was measured. The fecal water content was calculated from the difference between the fecal wet weight and the dry weight.

Drug-induced constipation in rats

SD rats weighing 233 – 326 g were used. After the administration of loperamide (5 mg/kg, p.o.) or clonidine (0.6 mg/kg, p.o.), both constipation producing agents, all of the feces expelled within 24 h was collected when observed. Observations for stool consistency, judgment for diarrhea and the weighing of feces were performed as described above. Test drugs or vehicles were administered orally 1 h before the administration of loperamide or clonidine.

Castor oil-induced diarrhea in rats

Wistar rats weighing 181 – 305 g were used. After the administration of castor oil (0.75 mL/animal), diarrhea (unformed feces) was observed. Since diarrhea was usually observed at about 1 h after dosing in preliminary studies, the effect of each drug was assessed by the reduction in the frequency of diarrhea during the 4-h period following dosing with caster oil. This time is 4 times the time to induce diarrhea and so allows us to evaluate delayed effects of the drugs tested. All feces expelled during the 4-h period were collected and the fecal water contents determined as described above. Drugs or vehicles were given orally 1 h before the administration of castor oil.

PGE_2-, 5-HT- and carbachol-induced diarrhea in mice

ICR mice weighing 21.7 – 34.3 g were used. After the administration of the diarrheogenic drugs prostaglandin (PG) E_2 (0.3 mg/kg, i.p.), 5-HT (3 mg/kg, i.p.) or carbachol (1 mg/kg, s.c.), the stool consistency was noted. The stools were graded into three consistency levels as follows: 0: normal, 1: soft, 2: unformed. Unformed stools were observed transiently only 1 or 2 times after treatment with PGE_2 and 5-HT and observed 2 or 3 times after carbachol. Soft or unformed stools were produced at around 15, 15 or 30 min after dosing PGE_2, 5-HT or carbachol, respectively, so the fecal consistency was observed for 1, 1 or 2 h after the dosing of PGE_2, 5-HT or carbachol, respectively (about 4 times the time to induction of diarrhea). The drugs or vehicles were given orally 1 h before the dosing of each diarrheogenic agent.

WRS model defecation in rats

Wistar rats weighing 213 – 305 g were used. To investigate the effect of drugs on stress-accelerated defecation, rats were subjected to WRS, a model of stress-related intestinal dysfunction without ulcer formation in IBS (11, 12). Rats were anesthetized lightly with ether and their shoulders, upper forelimbs and thoracic trunks were wrapped in cloth tape to restrict, but not prevent, movement. The animals awoke within 5 min and immediately moved about in their individual cages. The experiments were carried out between 4:00 and 6:00 PM to avoid any circadian influence

on stool excretion (11). One hour after administration of the test drug or vehicle, rats were subjected to WRS for 1 h. Williams et al. (11) reported that all feces were formed and dry, and restraint stress did not result in diarrhea; therefore, the wet weight of the fecal pellets expelled during the following hour was determined. Control animals were anesthetized with ether but were not wrapped.

Data analyses

The data are reported as the mean ± S.E.M. Williams' multiple range test was used for the statistical analysis of multiple comparisons within each group. Student's *t*-test for unpaired data was used when comparisons were made between two groups. Fisher's exact test for categorized data was used. The value of *P* of less than 0.05 was considered to indicate statistical significance.

Chemicals

The drugs used in this study were obtained from the following suppliers: Sigma, St. Louis, MO, USA (trimebutine maleate, carbachol and clonidine hydrochloride); Research Biochemicals Inc., Natick, MA, USA (loperamide hydrochloride); Nacalai Tesque Co., Kyoto (Carboxymethylcellulose sodium); Teijin, Osaka [Laxoberon (picosulfate sodium solution)]; Funakoshi Co., Tokyo (Prostaglandin E_2); Merck Japan, Tokyo (serotonin creatinine sulfate); and Wako Pure Chemical Industries Co., Osaka (castor oil). Polycarbophil was obtained by decalcification of calcium polycarbophil (B.I. Chemicals, Inc., Petersburg, VA, USA) and granisetron hydrochloride was synthesized in Hokuriku Seiyaku Co., Ltd. (Katsuyama).

Polycarbophil was suspended in saline. Trimebutine and granisetron were suspended in 0.5% w/v CMC solution. CMC, loperamide and clonidine were dissolved in distilled water. Picosulfate was diluted with saline and serotonin and carbachol were dissolved in saline. PGE_2 was diluted with saline after dissolving in ethanol. In order to avoid sudden expansion of the gastric wall, the administration volume was kept as less than 1.5 mL/100 g body weight, so that the maximum doses of polycarbophil and CMC were 1,000 mg/kg, this being the maximum possible to give through the catheter.

RESULTS

Effects on bowel movement in naive rats

Polycarbophil dose-dependently increased fecal weight (Fig. 1A) and water content (Table 1). Significant differences in fecal weight and water content were detected at doses greater than 500 and 250 mg/kg of polycarbophil, respectively; however, no diarrhea was observed. The effect of polycarbophil on fecal weight was evident within 16 h. CMC had no clear effect on daily fecal weight nor

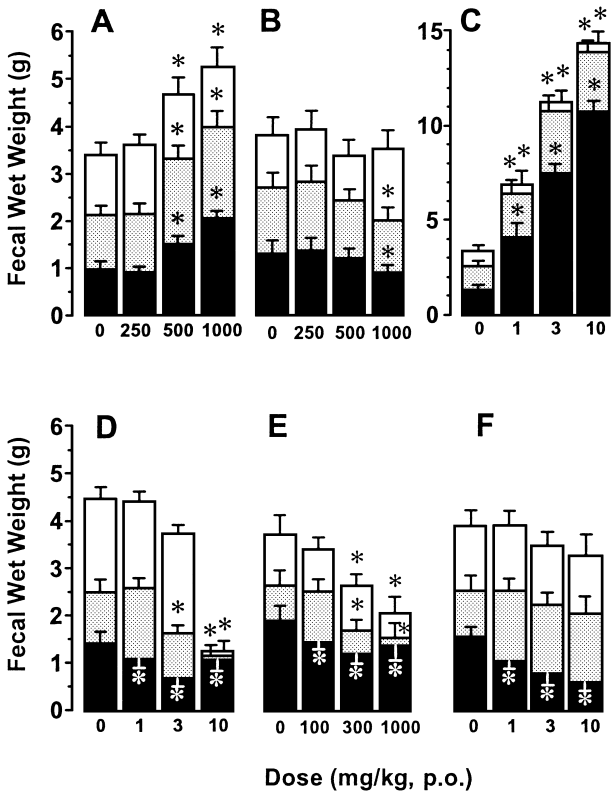

Fig. 1. Effects of polycarbophil (A), CMC (B), picosulfate (C), loperamide (D), trimebutine (E) and granisetron (F) on fecal weight in naive rats. The fecal weight is reported as the cumulative value over 0 – 8 h (solid columns), 8 – 16 h (gray columns) and 16 – 24 h (open columns) after oral administration of each drug. Note that the *Y* scale in the case of picosulfate is reduced. Values are reported as the mean ± S.E.M of 11 – 16 animals. The totalized fecal weight as 0 – 8 h, 0 – 16 h and 0 – 24 h were statistically analyzed. **P*<0.05 versus each vehicle (0 mg/kg).

stool consistency, although fecal weights were slightly reduced over 16 h (Fig. 1B and Table 1). Picosulfate, a stimulant laxative, dose-dependently increased fecal weight (Fig. 1C), water content (Table 1) and the incidence of diarrhea (Table 2). The effect of picosulfate in increasing fecal weight was marked within 8 h. Significant differences for fecal weight, water content and the incidence of diarrhea were detected at a dose of 1 mg/kg or more, indicating that the cathartic action of picosulfate was due to water accumulation in the intestine. Loperamide, an anti-diarrheal opiate, reduced the weight of feces expelled over 8 h at a dose of 1 mg/kg and over 16 h at a dose of 3 mg/kg. Loperamide at 10 mg/kg markedly reduced total stool output (Fig. 1D), although it slightly increased fecal water content (Table 1) without diarrhea. Trimebutine, a gastrointestinal propulsive agent, decreased fecal weight evacuated over 8 h at a dose of 100 mg/kg and total weight at the dose of 300 mg/kg or more (Fig. 1E), without any remarkable change in stool consistency or water content (Table 1). Granisetron, a potent and specific 5-HT_3 antagonist, dose-de-

Table 1. Effects of the drugs on fecal water contents in naive rats

Drug	Dose (mg/kg, p.o.)	Fecal water contents (%)
Polycarbophil	0	47.1 ± 1.1
	250	48.9 ± 0.9*
	500	55.3 ± 0.8*
	1,000	59.2 ± 1.3*
CMC	0	49.6 ± 1.1
	250	50.4 ± 0.9
	500	49.4 ± 0.9
	1,000	49.3 ± 1.2
Picosulfate	0	50.0 ± 1.4
	1	72.4 ± 1.9*
	3	78.8 ± 0.7*
	10	82.2 ± 0.7*
Loperamide	0	51.2 ± 0.7
	1	50.2 ± 0.9
	3	49.8 ± 0.9
	10	53.3 ± 1.3*
Trimebutine	0	49.3 ± 1.3
	100	50.3 ± 0.7
	300	48.9 ± 1.2
	1,000	50.7 ± 1.2
Granisetron	0	53.7 ± 1.4
	1	51.3 ± 1.2
	3	52.7 ± 1.3
	10	51.7 ± 1.8

The percentages of fecal water contents are the ratio of weight of water to wet weight of feces expelled within 24 h after each drug dosing. Values are reported as the mean ± S.E.M. of 11 – 16 animals. *P<0.05 versus each vehicle (0 mg/kg).

Table 2. Effect of picosulfate on diarrhea production in rats

Dose (mg/kg, p.o.)	Incidence of diarrhea (%)		
	Native rats	Constipation model	
		Loperamide	Clonidine
0	0	0	0
1	79*	21	0
3	100*	80*	13
10	100*	100*	81*

Diarrhea was observed during 24 h and judged when the fecal pellet became to be muddy or watery. Values are reported as the percentage of diarrhea produced in tested 13 – 16 animals. *P<0.05 versus each vehicle (0 mg/kg).

pendently decreased the weight of feces expelled over 8 h at the dose of 1 mg/kg or more (Fig. 1F), without changes in stool consistency or water content (Table 1).

Effects on drug-induced constipation

Clonidine reduced the weight of feces expelled over 16 h

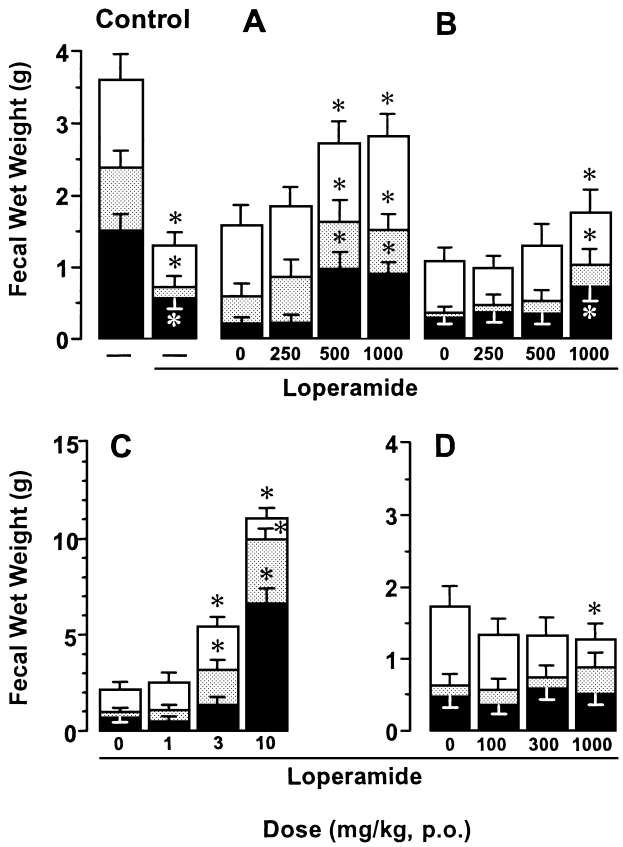

Fig. 2. Effects of polycarbophil (A), CMC (B), picosulfate (C), and trimebutine (D) on fecal weight in loperamide-induced constipation rats. The control animals received loperamide orally (5 mg/kg) or no treatment. The fecal weight is reported as the cumulative value over 0 – 8 h (solid columns), 8 – 16 h (gray columns) and 16 – 24 h (open columns) after the administration of loperamide. Note that the Y scale in the case of picosulfate is reduced. Values are reported as the mean ± S.E.M of 13 – 16 animals. The totalized fecal weight as 0 – 8 h, 0 – 16 h and 0 – 24 h were statistically analyzed. *P<0.05 versus each vehicle (0 mg/kg).

more markedly than loperamide and then increased rather than decreased the fecal weights in contrast to loperamide which continuously reduced them (Fig. 2, control and Fig. 3, control). Polycarbophil restored decreased fecal output dose-dependently and statistical significance was observed at the dose of 500 mg/kg or greater of polycarbophil. The effect of polycarbophil in increasing fecal weights was noticeable over 16 h in both models (Figs. 2A and 3A). Like polycarbophil, CMC significantly reverted fecal weights at a dose of 1,000 mg/kg in both models (Figs. 2B and 3B). CMC increased the weight of feces evacuated over 16 h. No diarrhea was observed after dosing polycarbophil or CMC. Picosulfate clearly increased fecal weights at doses of 3 and 10 mg/kg for loperamide- or clonidine-induced constipation, respectively (Figs. 2C and 3C). In the clonidine model, the fecal weights hardly recovered over 16 h after picosulfate, during which time defeca-

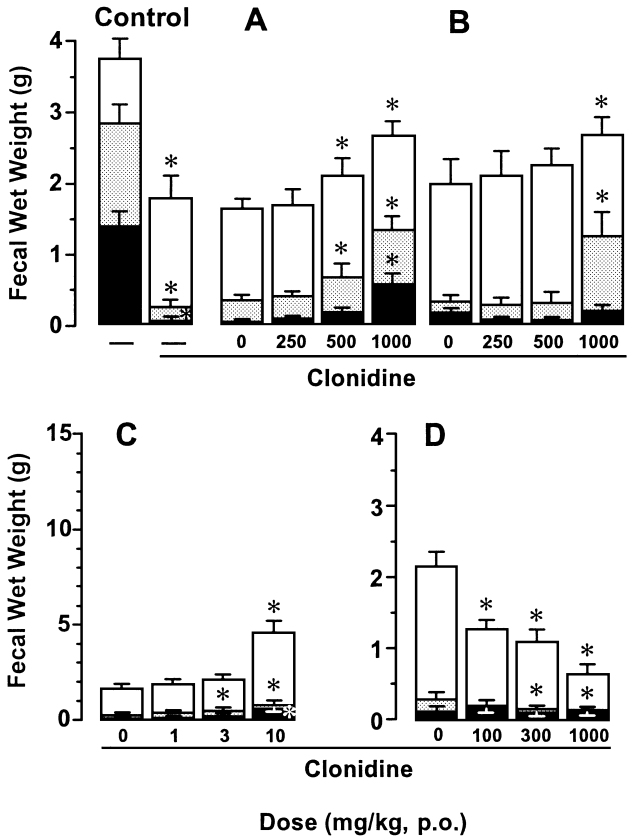

Fig. 3. Effects of polycarbophil (A), CMC (B), picosulfate (C), and trimebutine (D) on fecal weight in clonidine-induced constipation rats. The control animals received clonidine orally (0.6 mg/kg) or no treatment. The fecal weight is reported as the cumulative value over 0 – 8 h (solid columns), 8 – 16 h (gray columns) and 16 – 24 h (open columns) after the administration of clonidine. Note that the *Y* scale in the case of picosulfate is reduced. Values are reported as the mean ± S.E.M of 12 – 21 animals. The totalized fecal weight as 0 – 8 h, 0 – 16 h and 0 – 24 h were statistically analyzed. **P*<0.05 versus each vehicle (0 mg/kg).

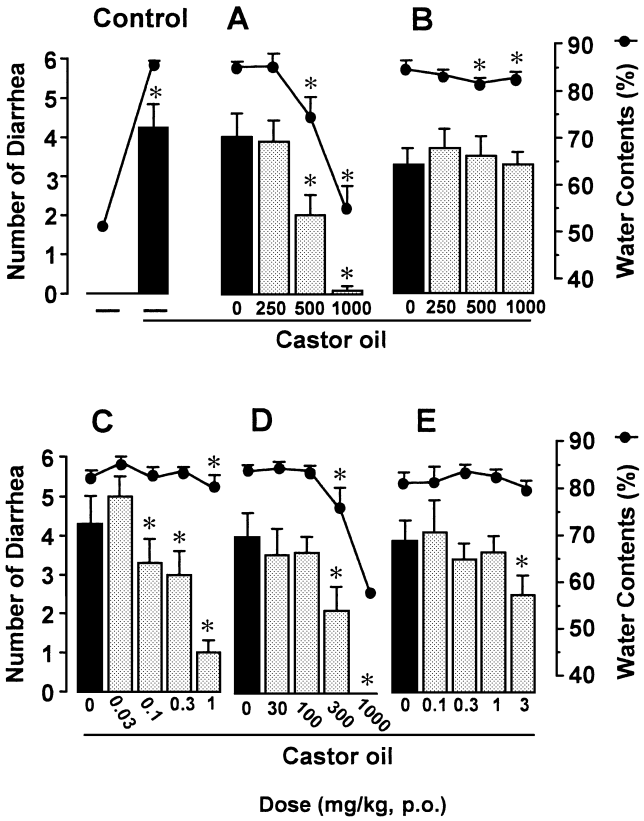

Fig. 4. Effects of polycarbophil (A), CMC (B), loperamide (C), trimebutine (D), and granisetron (E) on castor oil-induced diarrhea in rats. The control animals received castor oil orally (0.7 mL/animal) or no treatment. Diarrhea was observed during 4 h after the administration of castor oil. The number of diarrhea represents the number of watery or muddy feces, namely diarrhea, excretion. The percentage of fecal water contents expresses the ratio of weight of water to wet weight of feces evacuated during 4 h after the administration of castor oil. Only one animal defecated in the group of the untreated control and one in the group of 1,000 mg/kg of trimebutine; therefore the statistical analysis to water contents of each group could not be performed. Values are reported as the mean ± S.E.M. of 15 – 16 animals. **P*<0.05 versus each vehicle (0 mg/kg).

tion was strongly inhibited, although fecal weights clearly increased over a period of 16 – 24 h, in which clonidine had no affect on stool output. Picosulfate induced diarrhea at the same dose at which it increased fecal weights in both constipation models as it also did in naive rats (Table 2), demonstrating that the stimulatory effect of picosulfate on bowel movement was mainly due to increased water content. Trimebutine further decreased fecal weights at doses of 1,000 or 100 mg/kg in the loperamide and clonidine models, respectively, and no diarrhea was observed after trimebutine treatment (Figs. 2D and 3D). In the clonidine model, trimebutine clearly decreased fecal weights in the period of 16 – 24 h after dosing.

Effects on castor oil-induced diarrhea

The fecal water content was markedly increased and about a 4-times increase in diarrhea was produced by castor oil (Fig. 4 control). Polycarbophil decreased diarrhea and fecal water content dose-dependently, and this was statistically significantly different at a dose of 500 mg/kg of polycarbophil (Fig. 4A). CMC slightly reduced fecal water content, but had no effect on diarrhea up to the dose of 1,000 mg/kg (Fig. 4B). Loperamide significantly reduced diarrhea and fecal water content at doses of 0.1 and 1 mg/kg, respectively (Fig. 4C). Trimebutine decreased diarrhea and water content at a dose of 300 mg/kg and completely inhibited diarrhea at 1,000 mg/kg (Fig. 4D). Granisetron decreased diarrhea at 3 mg/kg without any changes in water content (Fig. 4E).

Effects on PGE_2-, 5-HT or carbachol-induced diarrhea

Almost all animals exhibited watery diarrhea after the

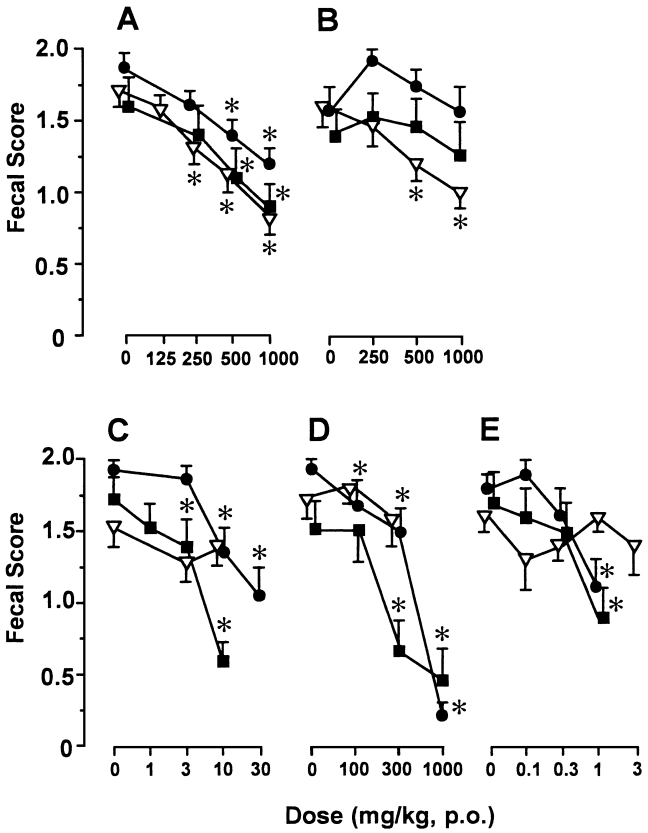

Fig. 5. Effects of polycarbophil (A), CMC (B), loperamide (C), trimebutine (D) and granisetron (E) on PGE_2 (solid circles)-, 5-HT (solid squares)- or carbachol (open triangles)-induced fecal consistency in mice. The stool consistency was observed during 1, 1 and 2 h after the administration of PGE_2, 5-HT or carbachol, respectively; and score of stool consistency was classified as follows: normal (0), soft (1) and watery (2). Diarrhea score represents most remarkable change in individual consistency of each feces in the observation period. Values are reported as the mean ± S.E.M of 13 – 17 animals. *P<0.05 versus each vehicle (0 mg/kg).

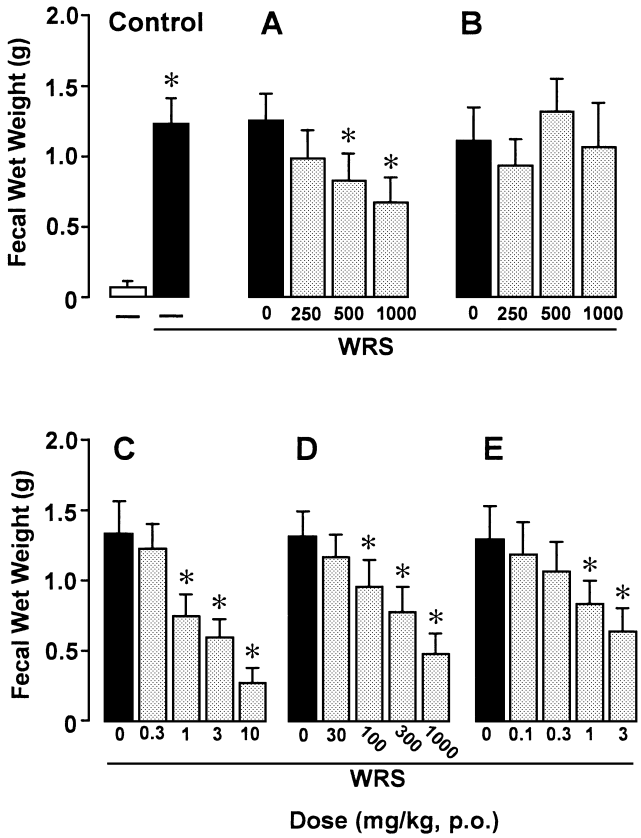

Fig. 6. Effects of polycarbophil (A), CMC (B), loperamide (C), trimebutine (D) and granisetron (E) on WRS-induced defecation in rats. The control animals were exposed WRS for 1 h or not. The feces expelled within 1 h after WRS exposition was weighed. Values represent the mean ± S.E.M. of 12 – 15 rats. *P<0.05 versus each vehicle (0 mg/kg).

dosing of each diarrheogenic agent. Polycarbophil dose-dependently produced formed stools in each diarrhea model, and statistical significance was observed at doses of 250, 500 and 500 mg/kg in carbachol-, PGE_2- and 5-HT-induced diarrhea, respectively (Fig. 5A). CMC produced formed stool in carbachol-induced diarrhea, but it showed no effect in diarrhea induced by other agents (Fig. 5B). Loperamide improved stool consistency at doses of 10 and 3 mg/kg in PGE_2- and 5-HT-induced diarrhea, respectively, but it had no effect on carbachol-induced diarrhea up to the dose of 10 mg/kg (Fig. 5C). Trimebutine improved diarrhea at doses of 100 and 300 mg/kg in the PGE_2 and 5-HT models, respectively, but like loperamide, it had no effect on carbachol-induced diarrhea (Fig. 5D). On the other hand, almost all animals used in the carbachol model died just after dosing 30 mg/kg of loperamide and 1,000 mg/kg of trimebutine, so that evaluations at these doses of drugs were not performed. Granisetron improved stool consistency at a dose of 1 mg/kg in the PGE_2 and 5-HT models, but it showed no significant effect in the carbachol model up to the dose of 3 mg/kg (Fig. 5E).

Effects on excretive response to WRS

Fecal weight was remarkably increased by WRS (Fig. 6, control), but diarrhea was not observed. No erosions in the gastrointestinal mucosa developed after 1 h of WRS. Significant dose-related decreases in the stimulated stool output were produced by polycarbophil, loperamide, trimebutine and granisetron; and statistical significance was observed at doses of 500, 1, 100 and 1 mg/kg, respectively (Fig. 6: A, C, D and E). CMC had no effect on WRS-stimulated defecation (Fig. 6B).

DISCUSSION

Fecal consistency best relates to the ratio of the water-holding capacity of the insoluble solids, such as those that

derived from dietary fiber, to the total water in the lumen (13). When there are sufficient water-holding solids and/or little non-bound (free) water, stools remain thick or formed. On the other hand, if there are too few of these water-holding solids to bind all of the water present, stool consistency becomes loose, eventually to the point of being like water (13). Except for the contribution to motility, many conventional laxatives, especially the stimulant and saline laxatives, and anti-diarrheal agents, can affect water absorption and/or secretion.

It has been reported that loperamide inhibits intestinal water secretion (14) and delays intestinal luminal transit (15 – 17). In this study, loperamide inhibited stool output and castor-induced diarrhea without changes in water content, demonstrating that the anti-diarrheal activity of loperamide is mainly based on its preventing intestinal luminal transit in rats. The loperamide-induced constipation model seems to be a spasm-produced constipation similar to the changes in intestinal motility with IBS. The α-adrenergic agonists also alter intestinal water absorption or secretion and motility (18). On the other hand, clonidine produces very little stimulation of absorption (19), suggesting that effects on motility are responsible for producing constipation. Clonidine affects intestinal motility by inhibiting the release of acetylcholine from cholinergic nerve terminals via stimulation of the α_2-adrenergic receptors (20). Therefore clonidine-induced constipation seems to be an atonic constipation model.

Polycarbophil, a synthesized high-molecular polymer, is insoluble and not absorbable from the intestine (21), so it cannot interact with any receptors except mechanoceptors, enzyme activity or signal transduction, and cannot change osmotic pressure in the lumen. Since unlike psyllium it is not metabolized by microorganisms, it does not cause formation of volatile fatty acids (6) nor does it stimulate intestinal secretion (22). If a hydrophilic polymer has much higher water-holding capacity as a solid, it might be expected to be not only a bulking laxative but also an anti-diarrheal agent. It is still unclear whether polycarbophil actually changes stool consistency, although the in vitro water absorbing power of polycarbophil has been reported (7). In our present data, polycarbophil improved constipation induced by loperamide or clonidine and diarrhea induced by various exogenous diarrheogenic agents as well as stool output endogenously mediated by restraint stress at the same dose. Polycarbophil increased fecal water contents without the induction of diarrhea in rats and formed stools loosened by diarrhea-related agents in mice, suggesting that it bonded a lot of free water and then strongly held the water against intestinal absorption. It is most improbable that the increased fecal weight was due to evacuated polycarbophil, because the administered polycarbophil at around 120 mg/animal (at a dose of 500 mg/kg) was much less than the increased fecal weight in naive rats. These results indicated that polycarbophil has potential for the treatment of both constipation and diarrhea as it normalized the consistency of the luminal contents and/or feces by its swelling and gelling properties based on its remarkable water holding capacity. In addition to the change in stool consistency, polycarbophil accelerated intestinal luminal transit, producing increased fecal weight in the first 8 h after dosing in naive and constipated rats. There is also the possibility that polycarbophil delayed intestinal luminal transit in the diarrhea models, as polycarbophil decreased stool output stimulated by WRS, which increases stool output by altering intestinal transit without increasing fecal water content (11). Further investigation regarding the effect of polycarbophil on intestinal luminal transit should be done. On the other hand, the abdominal pain and discomfort at onset are associated with a change in stool consistency and frequency and relieved by defecation (1), so that there is a hope of indirect improvement of the symptoms based on normalization of stool consistency and frequency by polycarbophil.

CMC slightly increased fecal weight in constipated rats, while it did not show any marked effect on stool output in naive rats. In the diarrhea models, CMC had no effect in any model except for carbachol-induced diarrhea. Polycarbophil and CMC are classified as bulk-forming laxatives, but these results indicated that the pharmacological characteristics of both agents are different. CMC is soluble and therefore it cannot gel. The viscosity, as an indicator of fluidity, of a CMC solution is markedly less than that of a polycarbophil emulsion; for example, 1% w/v polycarbophil shows the same viscosity as 2% w/v CMC (7). The pharmacological difference between polycarbophil and CMC may be due to the viscosity based on the gel-forming properties. In fact, CMC was effective in constipation and the carbachol-induced diarrhea model at twice the dose of polycarbophil, and CMC might have been effective also in the models where it showed no activity if it had been possible to administer higher doses. On the other hand, polycarbophil and CMC improved stool consistency in carbachol-induced diarrhea at lower doses than in the other models. We have confirmed that carbachol, but not PGE_2 and 5-HT, shortened whole-gut transit time (data not shown). Intestinal motility rather than water secretion might contribute to the induction of diarrhea in the carbachol model we used, in view of the late onset and long duration of the diarrhea observed, so this model may be sensitive to change in viscosity of the intestinal luminal contents.

Colonic bacteria hydrolyze a diphenylmethane derivative of picosulfate, and then an active moiety stimulates intestinal motility and secretion (23). In our present study, picosulfate induced diarrhea at the same dose that increased

fecal weight, demonstrating that the laxative effect of picosulfate was clearly related to production of diarrhea. Additionally, high doses of picosulfate were needed to increase fecal weight, correlating with the severity of the constipation in our models. These results support that some colic and liquid stools tend to result from the dose used clinically, and it is difficult to adjust the dose to produce just soft or formed stools as discussed by Lennard-Jones (23).

Loperamide inhibited diarrhea caused by various agents and also the stool output stimulated by WRS in the present study, as previously reported (24, 25). In our study, effective doses of loperamide were very variable with a 100 times difference between the different diarrhea models. Additionally, loperamide prevented bowel movements at the same dose that inhibited diarrhea in naive rats, suggesting the possibility of inducing constipation while trying to treat diarrhea.

Trimebutine is effective for various symptoms including abdominal pain, nausea and IBS (26). The usual dose of trimebutine inhibits cholinergic and adrenergic neurons by activating the opiate-μ and κ receptors, resulting in a dual effect on intestinal motility (27, 28). For its regulative effects on bowel movement, it was reported that trimebutine inhibited experimental diarrhea in mice and rats (29, 30). Also in our present study, it prevented diarrhea and WRS-induced defecation, but our data did not show any therapeutic potential for the treatment of constipation. These results suggest that trimebutine is more effective for the treatment of diarrhea than for constipation. It has been reported that colonic transit time was reduced only in patients with delayed colonic transit and was slightly increased in patients with normal colonic transit (31). Careful selection of patients is needed, though difficult, if trimebutine is to be prescribed for constipation. Almost all animals died following a high dose of trimebutine as occurred with loperamide, which is hardly distributed to the brain (24), in the carbachol-induced diarrhea model, suggesting that there might be some interaction between the opiate and muscarinic receptors in the peripheral nervous system.

Recently attention has focused on the 5-HT_3 receptors because of their apparent roles in visceral pain and motility (5, 32). Hypersensitivity of the gut may be a characteristic of the irritable bowel, as well as other functional gastrointestinal disorders, and 5-HT_3-receptor antagonists can inhibit excitation of the extrinsic sensory nerves by 5-HT (33) and rectal distension (5, 34). It has been reported that a selective and potent 5-HT_3-receptor antagonist, granisetron, increased tolerance to colonic distention and reduced rectal sensitivity in IBS patients (35). Ample evidence indicates that 5-HT_3 receptors within the myenteric plexus are involved in augmenting peristalsis through stimulating the cholinergic and tachykininergic excitatory pathways (36, 37). Therefore, antagonism of the 5-HT_3 receptors may be useful in treating functional bowel disease because of their possible inhibitory activity on hypermotility and/or hypersensitivity. In this study, while granisetron strongly inhibited many kinds of diarrhea, it decreased stool output in naive rats, supporting that constipation tend to result from the clinical use of 5-HT_3-receptor antagonists (38, 39).

Consequently, it was considered that polycarbophil has laxative activity while not inducing diarrhea and also has anti-diarrheal activity while not producing constipation, which is different from the other agents used in this study. It seems evident that polycarbophil is useful for the treatment of FBD, especially IBS with alternating constipation and diarrhea, because of the reduced side effects such as diarrhea or constipation. The insoluble polymers, which have marked water-holding capacity and gel-forming properties such as carbophil compounds, will be promising for the treatment of FBD.

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