Calcium Polycarbophil, a Water Absorbing Polymer, Increases Bowel Movement and Prevents Sennoside-Induced Diarrhea in Dogs

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ABSTRACT—The effects of calcium polycarbophil (CP), a water-absorbing polymer, on bowel movement were examined in comparison with known laxatives and anti-diarrheal agents in dogs, a species that resembles humans for stool output. CP increased stool frequency, fecal water content and fecal weight in a dose-dependent manner, but did not induce diarrhea. Sennoside and carboxymethylcellulose sodium (CMC-Na) increased fecal water content and induced diarrhea at lower doses than that which enhanced stool frequency. Trimetaphine decreased stool frequency, fecal weight and fecal water content, resulting in inhibition rather than stimulation of defecation. In sennoside-induced diarrhea, loperamide and CP improved stool consistency and this was accompanied by reduced fecal moisture and frequency of diarrhea. In contrast, CMC-Na aggravated stool consistency with increased fecal water content and frequency of diarrhea, and trimetaphine had little noticeable effect apart from reducing fecal weight. Our results show that CP has both laxative and anti-diarrheal effects in dogs and differed from conventional laxatives and anti-diarrheal agents. CP may be a suitable agent for treatment of idiopathic constipation, secretory diarrhea and irritable bowel syndrome with alternating constipation and diarrhea and with either predominating in terms of less side effects such as diarrhea or constipation.

Keywords: Constipation, Diarrhea, Water absorbing polymer, Calcium polycarbophil

Irritable bowel syndrome (IBS) is recognized widely as one of the most commonly encountered gastrointestinal disorders in the United States and Europe, even though lower prevalence has been reported in Asia and Africa (1). IBS is a motor disorder clinically consisting of altered bowel habits, abdominal pain or discomfort, and the absence of any detectable organic pathologic process (1). Although the precise etiologic basis of IBS is not known, it is assumed that IBS is a complex disorder with physiologic and psychosocial components in which altered motility or sensation in the intestine are modulated by input from the central nervous system (2). The disturbance in bowel function is gradually progressive, eventually developing a characteristic pattern, most commonly alternating constipation and diarrhea, with either predominating (1). The abdominal pain or discomfort is associated with a change in frequency and/or consistency of stool and is relieved by defecation (3). Because of the variety of the symptoms and as drugs are rarely of benefit for all patients with IBS, medication has been best delivered in an individualized manner and tailored to each patient’s needs (1).

CP is the calcium salt of polyacrylic acid cross-linked with divinylglycol (4) and is classified as a bulk-forming agent (5). Because of its hydrophilic properties, it is considered that CP binds water in the lumen of the intestinal tract and thus prevents excessive lumping or looseness of the stools (4). Therefore, CP may be effective for both constipation and diarrhea. Although the clinical usefulness of CP has been reported (6–10), there are not enough reliable reports obtained from well-controlled clinical studies. To our surprise, even in experimental animals, the laxative and anti-diarrheal effects of CP have not yet been demonstrated. If CP is shown to be effective for both constipation and diarrhea, it might be suitable for IBS patients complaining of not only either predominating but also alternating constipation and diarrhea. Reliable data for CP in experimental animals may promote the undertaking of well-controlled clinical studies of CP to clarify the potential of CP for the treatment of IBS.

The aim of this study was to evaluate stimulatory and inhibitory effects of CP on bowel movement in dogs in comparison with conventional agents used for treating constipation, diarrhea and IBS. To evaluate the laxative and anti-diarrheal effects of each agent in detail, not only stool
consistency, obtained by scoring, and the induction of diarrhea, but also the frequency of bowel movement, fecal weight and moisture were measured.

MATERIALS AND METHODS

Animals

Adult beagle dogs of either sex weighing 7.9 – 12.0 kg (Oriental Yeast Co., Ltd., Tokyo) were used. Animals were individually housed and allowed to acclimate to standard controlled environmental conditions of temperature (20 – 26°C) and air humidity (30 – 70%) with 12-h light/dark cycles for at least 2 weeks before the start of the experiment. Animals were given 240 g of solid food for laboratory dogs (Oriental Yeast Co., Ltd., Tokyo), providing adequate nutrition (369 kcal/100 g including crude protein: 25.7%, crude fat: 8.6%, dry matter: 7.3%, crude fiber: 4.3% and nitrogen-free extract: 47.3%), once a day until start of the experiments to maintain their physical condition. From at least 2 days before the start of the experiment until the end of the experiment, daily food was equally divided into 3, and 80 g each was given to the animals every 8 h (at 8:00, 16:00 and 0:00). Animals ate the meal completely within 30 min. Water was available ad libitum also during the experiment period. Animals were randomly put into groups in such a way that there was no bias according to weight and sex, and experiments were performed with at least 5-day intermissions.

Effect on bowel movement

Figure 1 shows the experimental schedule for each drug. A stimulant laxative, sennoside was given orally 4 h after feeding at doses of 10, 30, 100 mg/kg, and evaluation of bowel movement was continued for 24 h after dosing. CP, a bulking agent, is recommended for repeated treatment and to be taken with meals (1). Thus, it was orally administered 30 min after every feeding for 3 consecutive days at doses of 167, 333 and 667 mg/kg. The evaluation of bowel movement was started 24 h before the first dose and continued during the treatment period and following 48 h after the last dosage. CMC-Na, another bulking agent, and trimubutine, a gastrointestinal propulsive agent, were used in a repeated manner in the same way as CP. CMC-Na was orally administered 30 min after every feeding for 2 consecutive days at doses of 167, 333 and 667 mg/kg. The evaluation was carried out during the 2nd day of the repeated administration period. Trimubutine was orally administered 30 min after every feeding at doses of 10, 30 and 100 mg/kg, and the evaluation was done for 24 h after the first dose.

The feces were collected just after evacuation and graded into four consistency levels as follows: formed: stool maintains shape; soft: all or part of the stool is soft but not muddy; muddy: all or part is starchy and pours slowly; watery: pours and spreads rapidly, without attribution to any dog or drug by a technician who was unaware of which of these drugs were prescribed. When the feces became muddy or watery, this was judged to be diarrhea. To obtain further information on the bowel movement, fecal weight and fecal moisture were also measured. Feces were collected and weighed when seen, and then dried for more than 24 h at 70°C in a ventilated oven. The fecal water content was calculated from the difference between the fecal wet weight and dry weight, and the fecal moisture percentage was obtained as the ratio of fecal water content to fecal weight.

Effect on sennoside-induced diarrhea

Figure 2 shows the schedule of the experiment on the anti-diarrheal effect of each drug. Diarrhea was induced by the single oral administration of 100 mg/kg of sennoside at 4 h after feeding, and evaluation was performed for 12 h after the administration of sennoside, since the stimulatory effect of sennoside was found to be almost abolished within 12 h. Loperamide was orally given to dogs 2 h prior to the administration of sennoside at doses of 0.1 and 0.3 mg/kg.
Fig. 2. Experimental schedules to evaluate the effect of each drug on sennoside-induced diarrhea in dogs. a: Loperamide was given by single oral administration 2 h before sennoside dosing. b, c: CP and CMC-Na were given orally 30 min after 4 consecutive feedings at 8-h intervals. Sennoside was administered orally 4 h before the last dosing. d: Trimebutine was orally given 2 h before and 2 h after dosing with sennoside, between feedings. Observation and collection of feces were done for 12 h after dosing with sennoside. Drug administration and feeding is indicated by the symbols ▽ and ●, respectively. The observation period is indicated by the horizontal open bar above each scale.

CP and CNC-Na were orally administered 30 min after each 4 consecutive feedings, namely at 20, 12 and 4 h before the administration of sennoside and at 4 h after the administration because CP and CMC-Na were found to affect the bowel movement on the day following the first dosing as shown in the result of the experiment on bowel movements. The doses of CP and CMC-Na were 167, 333 and 667 mg/kg and 333 and 667 mg/kg, respectively. Trimebutine was given orally 2 h before and 2 h after the administration of sennoside at doses of 10, 30 and 100 mg/kg.

The classification of stool consistency, judgment to be diarrhea, fecal weight and fecal moisture percentage were investigated by the same method as described above. The incidence of diarrhea was obtained as a percentage of the diarrheal incidences to the total number of bowel movements for each dog. Not only the mean but also the maximum fecal moisture, which was the highest percentages and expressed worst stool consistency for each dog, were evaluated because the mean fecal moisture might not have been noticeably changed when only small feces contained a high amount of water, and furthermore, severe watery stool would produce much discomfort to patients with diarrhea even if this occurred only once a day.

Drugs
Calcium polycarbophil (B.I. Chemicals, Inc., Petersburg, VA, USA), sennoside (including both sennoside A and B; Nippon Funmatsu Yakuhin Co., Ltd., Osaka), carboxymethylcellulose sodium (Nacalai Tesque, Inc., Kyoto), loperamide hydrochloride (Research Biochemicals International, Natick, MA, USA) and trimebutine maleate (Sigma Chemical Co., St. Louis, MO, USA) were purchased. Each drug was put into gelatin capsules (Torpac, Fairfield, NJ, USA) and administered orally. As a control, the same number of empty capsules was given.

Statistics
The classification of stool consistency was analyzed by the 1 way cumulative chi-squared method. Other results were expressed as the mean ± S.E.M. and statistically analyzed by means of the Williams’ multiple range test. P values less than 0.05 were considered to be statistically significant.

RESULTS

Effect on bowel movement
Sennoside at a dose of 10–100 mg/kg, p.o. made the stools loose and produced a dose-related diarrhea (Fig. 3A). As shown in Fig. 4, the fecal wet weight, fecal water content and fecal moisture were dose-dependently increased; however, a significant increase in stool frequency was only observed at the highest dose, showing that changes in fecal form preceded the increase in stool frequency. Sennoside had no effect on fecal dry weight, demonstrating that the stimulatory effect of sennoside on bowel movement was mainly due to increased water content.

CP had no effect on stool consistency in dogs (Fig. 3B), and CP at a dose of 167 mg/kg, 3 times a day, produced no changes in bowel movement during the experiment period. However CP at 333 and 667 mg/kg, 3 times a day, significantly increased stool frequency, fecal wet weight, dry weight and water content during the treatment period (Fig. 5). Since CP is not absorbed from the intestine, the increase of fecal dry weight seemed to be due to the presence of CP itself in the feces. Contrary to our expectation, fecal moisture was slightly decreased by CP at doses of 333 and 667 mg/kg, 3 times a day (Fig. 5). These changes induced by CP almost completely disappeared within 2 days after cessation of dosing (Fig. 5).

CMC-Na at doses of 167–667 mg/kg, 3 times a day, produced loose stools dose-dependently and induced diarrhea (Fig. 3C). CMC-Na also significantly increased fecal wet weight, fecal moisture, fecal dry weight and fecal water content even at the lowest dose; however, stool frequency was only increased by the highest dose of CMC-Na (Fig. 6A). The results indicate that stool frequency was not affected, unlike the fecal properties. Based on the fact that CMC-Na is unabsorbed from the intestine, it was likely
that the increase of fecal dry weight was partly due to the evacuation of the actual CMC-Na as with CP.

Trimebutine did not affect stool consistency (Fig. 3D). However, it decreased stool frequency, fecal wet weight, fecal dry weight and fecal water content at a dose of 100 mg/kg, 3 times a day (Fig. 6B). Trimebutine seemed to have an inhibitory effect on bowel movement, but the fecal moisture was maintained at a level similar to the control level (Fig. 6B).

**Effect on sennoside-induced diarrhea**

Single oral administration of sennoside at a dose of 100 mg/kg significantly increased fecal moisture as shown before (Fig. 4). With regard to the time course for the stimulatory effect of sennoside, as shown in Fig. 7, the fecal moisture suddenly reached the maximum (around 90%) at around 4 h after oral dosing of 100 mg/kg sennoside and then gradually returned to the control level (around 75%) within about 12 h. All the dogs treated with 100 mg/kg of sennoside showed diarrhea during this 12-h period. After that, conspicuous diarrhea was not observed; therefore, the evaluation of the anti-diarrheal efficacy of each drug was done for the 12 h after dosing with sennoside.

Loperamide formed the loose feces caused by sennoside (Fig. 8A). Coinciding with the improvement of stool consistency, diarrhea frequency, diarrhea rate, fecal wet weight, fecal moisture and maximum fecal moisture decreased at a dose of 0.3 mg/kg (Fig. 9A). Loperamide did not reduce the stool frequency at up to 0.3 mg/kg (Fig. 9A).

CP formed feces loosened by sennoside in a similar way to loperamide (Fig. 8B). CP at doses of 333 mg/kg, 3 times a day, decreased the rate of diarrhea; and at 667 mg/kg,
Fig. 5. Effects of repeated treatment with CP on bowel movement in dogs. Each value expresses the mean ± S.E.M. of 10 dogs. The mean values of stool frequency, fecal wet weight, moisture percentage, dry weight and water content before dosing with CP were 4.7 times, 256 g, 74.7%, 64 g and 191 g, respectively. CP (▼) was administered orally 3 times a day at doses of 167 mg/kg (▲), 333 mg/kg (■) and 667 mg/kg (●), and empty capsules were given as the control (0 mg/kg, ○). *P<0.05 vs control value on each day determined by Williams' multiple range test.

Fig. 6. Effects of CMC-Na (A) and trimebutine (B) on bowel movement in dogs. Each value is the mean ± S.E.M. of 10 dogs. *P<0.05 vs control (0 mg/kg, empty capsule) determined by Williams' multi range test.
3 times a day, it decreased the frequency of diarrhea, fecal moisture and maximum fecal moisture in addition to the rate of diarrhea (Fig. 9B). Stool frequency and fecal wet weight were not changed by CP (Fig. 9B). Although it was impossible to measure the weight of CP mixed with stools, it seemed that CP by binding to a large amount of water interfered with the reduction in fecal wet weight. If the dose levels and the mode of action are ignored, CP seemed to resemble loperamide in its effect on sennoside-induced diarrhea.

In contrast to CP and loperamide, CMC-Na changed the consistency of feces to become more loose (Fig. 8C). Coinciding with aggravation of the stool consistency, it increased stool frequency and the frequency of diarrhea at 167 mg/kg, 3 times a day; fecal wet weight at 333 mg/kg, 3 times a day; and fecal moisture and the rate of diarrhea at 667 mg/kg, 3 times a day (Fig. 9C). This clearly demonstrated that CMC-Na aggravated diarrhea in sennoside-treated dogs, and thus it differed from CP.

Trimetobutine had no effect on stool consistency (Fig. 8D). It decreased fecal wet weight at 100 mg/kg, twice a day but failed to affect the other characteristics (Fig. 9D). Although trimetobutine is an opiate agonist as is loperamide, it showed no anti-diarrheal effect at the doses used in this study.

**DISCUSSION**

It has been reported that the frequency of bowel movement is 3–21 times/week (0.5–3 times/day), and fecal wet weight is 100–500 g/day in healthy people, although the quantity of stool output in humans widely varies according to the individual, race and dietary intake (5). On the other hand, the percentage of moisture in the feces has been reported to be approximately 70% in healthy people (11). Under our experimental conditions including daily 3 times feeding in dogs, stool frequency, fecal wet weight and fecal moisture were 4.7 times, 256 g and 74.7%, respectively. Stool frequency of our dogs was relatively higher than that of humans, but fecal wet weight and fecal moisture were similar to those of humans. In diagnosing constipation and diarrhea, it is necessary to take into consideration not only frequency and/or quantity of stool but also consistency of feces (5, 12). Therefore dogs seem to be suitable for studying the effect of several drugs on bowel movement as a human-like model.

Sennosides are hydrolyzed to the anthrol, the active metabolite, by bacteria in the gut (13), and their cathartic
action appeared as the result of stimulation of water secretion, restraint of water absorption and/or promotion of gastrointestinal motility (14–17). In this study, senoside showed cathartic action in dogs at doses of 10–100 mg/kg, p.o. The laxative action of senoside in dogs may be mainly contributed by intraluminal water accumulation rather than intestinal motor stimulation, since the dose to increase stool frequency was 10 times higher than that to decrease stool consistency. In addition, the laxative action of senoside was found to be equal to the degree of induction of diarrhea, so that diarrhea would be unavoidable in treating constipation.
CMC-Na is a commonly used bulk-forming laxative, and is not a stimulant laxative. It is also classified as an unabsorbable soluble dietary fiber, and it is considered that CMC-Na relieves constipation due to its water absorbing and bulk-forming characteristics (5). In our present study, CMC-Na induced loose stools and increased fecal moisture in naive dogs and aggravated diarrhea in sennoside-treated dogs. Although CMC-Na is recommended for long-term therapy (5), it seemed to relieve constipation probably though the induction of diarrhea in the same way as sennoside.

Loperamide is a widely used anti-diarrheal agent and an opiate receptor agonist, which inhibits intestinal water secretion and delays an accelerated intestinal transit (18–22). Our study clearly showed that 0.3 mg/kg loperamide prevented sennoside-induced secretory diarrhea in dogs.

Trimebutine, a gastrointestinal propulsive agent used in the treatment of IBS and functional dyspepsia, has been reported to interact with the opiate receptor within the intestine (23, 24). It was reported that trimebutine had stimulatory and inhibitory effects on gastrointestinal motility in isolated guinea pig ileum (25), and improved delayed colon transit and suppressed accelerated colon transit in rats (26). It was also reported that trimebutine inhibited experimental diarrhea in rats (27, 28). In this study, trimebutine at a dose of 100 mg/kg decreased stool frequency and fecal weight in naive dogs and also decreased fecal weight in sennoside-treated dogs, suggesting that trimebutine might have an anti-diarrheal effect in dogs. However, our data could not show any therapeutic potential for the treatment of constipation. Schang et al. (29) stated that trimebutine is useful in constipated patients who show signs of delayed colonic transit, but is not effective in patients with normal transit. These findings suggest the possibility of inducing constipation in conditions of normal colonic motility by treating with trimebutine.

CP is a synthesized high-molecular weight polymer. It is considered that CP relieves constipation and inhibits diarrhea due to the remarkable water holding capacity and/or gel forming properties of polycarbophil, an active form of CP, which is produced by decalcification of CP under acidic conditions such as in gastric juice (4, 30, 31). Yamada et al. (32) reported that polycarbophil reduced water influx without altering water efflux, resulting in a reduction of net water flux in the in situ rat intestine. Polycarbophil binds large amounts of water in the lumen of the intestinal tract, and thus, in constipation, the swelling properties of polycarbophil seems to contribute to the intraluminal stimulation of evacuation, and in diarrhea, its gelling properties seem to contribute to the improvement of the diarrheal stool consistency and the restraint of accelerated intestinal transit. In our present study, CP increased fecal wet weight together with fecal water content in naive dogs, suggesting that CP bound a large amount of water and was evacuated within the feces. The increase in fecal dry weight strongly supports our interpretation. CP increased stool frequency in a dose-dependent manner but induced no diarrhea and so differed from sennoside and CMC-Na. This suggests that the expanded CP accelerated intestinal propulsion and held an increased water content not as free water but as bound water. All the data obtained from naive dogs indicated that CP has therapeutic potential for the treatment of constipation without the induction of diarrhea. Although CP reduced the fecal moisture percentage to 72% in naive dogs, it is unlikely that CP will produce constipation, considering that the feces of patients complaining of constipation contain only 40–60% water (11). With respect to the anti-diarrheal effect of CP, it improved the consistency of feces and decreased the frequency of diarrhea and fecal moisture in sennoside-treated dogs at the same dose range showing stimulatory effects on bowel movement in native dogs. CP and CMC-Na are classified as bulk-forming laxatives, but this data clearly indicated that the pharmacological characteristics of both agents are completely different. CMC-Na is soluble, and on the other hand, CP is insoluble and gels after water binding. This physicochemical difference might cause the difference in efficacy between CP and CMC-Na.

Consequently, CP was considered to be a laxative agent inducing no diarrhea and also an anti-diarrheal agent producing no constipation, which is different from the other agents used in this study. It seems evident that CP has potential for the treatment of both constipation and diarrhea, CP will be a promising agent to treat IBS patients with alternating constipation and diarrhea or with either predominating in terms of less side effects such as diarrhea or constipation.

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