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Gastroprokinetic effects of DA-9701, a new prokinetic agent formulated with Pharbitis Semen and Corydalis Tuber

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Abstract

To develop a therapeutic for functional dyspepsia (FD), a prokinetic agent, DA-9701 has been newly formulated with Pharbitis Semen and Corydalis Tuber and we evaluated the gastroprokinetic effects of DA-9701 in comparison with conventional prokinetics. Oral administration with DA-9701 not only significantly accelerated gastric emptying in normal rats but also restored the delayed gastric emptying caused by apomorphine and cisplatin up to almost normal levels. For gastrointestinal transit, DA-9701 caused FITC-dextran to travel a significantly longer distance than the control, and in the delayed GI transit models induced by laparotomy and atopine, DA-9701 considerably increased the values of mean geometric center (MGC), while the conventional prokinetics rarely showed significant effects. Furthermore, DA-9701 drastically increased the gastric accommodation in Beagle dogs, shifting the pressure–volume curve toward considerably higher volume compared to the control, which was comparable to that of cisapride. These results indicate that DA-9701 has potential as a safe and effective therapeutic for FD patients with abnormalities in GI motor function.

Keywords: DA-9701; Pharbitis Semen; Corydalis Tuber; Prokinetics; Functional dyspepsia

Introduction

Functional dyspepsia (FD), newly defined as persistent or recurrent postprandial distress syndrome (PDS; early sensation or postprandial fullness) and epigastric pain syndrome (EPS; pain and discomfort or burning in the epigastrium), is a common pathology of the gut (Karamanolis et al., 2006). The pathophysiology of FD is complicated with multifactors including abnormal motility, visceral hypersensitivity, psychological factors, and disturbed brain–gut interaction (Tack et al., 2004); however, abnormalities in gastrointestinal (GI) motor functions has been proposed as a major cause for FD among others. In point of fact, delayed gastric emptying and meal transit has not only been reported in 30–40% of FD patients (Talley et al., 2006) but also a number of studies have demonstrated impaired accommodation of the proximal stomach to a meal in roughly 40% of FD patients (Tack, 2000). Prokinetic drugs enhancing GI motor function through acting on a variety of

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neurotransmitter receptors has been used for FD patients (Galligan and Vanner, 2005), and regarded as one of the most efficacious therapeutics for this disorder (Hiyama et al., 2007). Cisapride, stimulating GI motor activity from stomach to colon and enhancing gastric accommodation (Yoshida et al., 1991; Tack et al., 1998), was one of the most widely used prokinetics; however, the use of this drug is now restricted due to serious adverse cardiac arrhythmias (Flockhart et al., 2000). Mosapride citrate, another widely used gastroprokinetic drug accelerating upper GI motility (Mine et al., 1997), has been regularly used, but the efficacy data is conflicting (Hallerback et al., 2002). Furthermore, domperidone, a dopaminergic antagonist, may be useful in the management of FD symptoms (Halter et al., 1997), but is not licensed in the US for FD (Reddymasu et al., 2007), and associated with side effects such as cardiac arrhythmia (Drolet et al., 2000) and galactorrhea (Cann et al., 1983). Itopride was reported to significantly improve global dyspeptic symptoms (Holtmann et al., 2006); however, a recent European phase III trial failed to confirm its efficacy in the treatment of FD. Therefore, there has been an increasing need for the development of safer and more effective gastroprokinetic agents. To develop novel therapeutics for FD we selected 15 herbs based on traditional herbal medicinal theories and clinical records, which were expected to assist with a variety of digestion problems, and screened their effects on GI motor function using several *in vivo* experiments. The seed of *Pharbitis nil* Choisy (Pharbitidis Semen, Convolvulaceae) has been used as a folk medicine for analgesic effects on the abdomen in the Chinese traditional medicine. Pharbitidis Semen has been found to possess gibberellins and resin glycosides (Takahashi et al., 1969; Ono et al., 1990). The root of *Corydalis yahusuo* W.T. Wang (Corydalis Tuber, Papaveraceae) has been used as a folk medicine for analgesic and anti-ulcer effects in the Chinese traditional medicine. Extracts from Corydalis Tuber have been reported as having several biologic activities such as a antispasmodic agent for gastrointestinal tract and analgesics (Ma et al., 2000); however, pharmacological effects on GI motor function has hardly been studied. In our preliminary experiments these two herbs indicated remarkable effects on GI motor function. Here we show the possibility of DA-9701 as a new prokinetic agent.

Materials and methods

Preparation of DA-9701

DA-9701 is the standardized extract of the seed of *Pharbitis nil* Choisy (Pharbitidis Semen, Convolvulaceae) and the root of *Corydalis yahusuo* W.T. Wang (Corydalis Tuber, Papaveraceae). These two herbs were purchased at a Kyungdong herbal market, Seoul, Korea and confirmed by an emeritus Prof. Changsoo Yook (Kyung Hee University, Korea). Dried Pharbitis Semen and Corydalis Tuber were mixed (3 kg), and extracted with 50% aqueous EtOH (24 l) three times at room temperature for 48 h. After filtration, the aqueous EtOH extract was evaporated under reduced pressure to yield brown extract (250 g, named DA-9701). The standard method evaluating the quality of DA-9701 has been established using quantitative HPLC. The contents of at least three compounds, the alcaloids corydaline and palmatine for *Corydalis yahusuo* and chlorogenic acids for *Pharbitis nil* in DA-9701 were determined.

Chemicals

Atropin, cisplatin, apomorphine, cisapride, domperidone, phenol red, and hydroxypropylmethyl cellulose (HPMC) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Mosapride citrate was synthesized at Dong-A Pharm. Research Labs, and the purity of the drug was more than 99.7%, which was confirmed by HPLC analysis before use. Itopride and FITC-Dextan were purchased from Choongwae Pharma (Seoul, Korea) and Fluka (Tokyo, Japan), respectively.

Animals and experimental procedure

Male Sprague–Dawley rats (200–220 g) were purchased from OrientBio, Inc. (Gapyeung, Korea) and Beagle dogs were purchased from Central Lab. Animal Inc. (Seoul, Korea), individually housed in single, air conditioned boxes and given dog food in pellet form (Purina, Dog Chow®). All experimental procedures were conducted according to the principles enunciated in the Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animal Resources, National Research Council (http://www.nsa.edu/nrc). Animals were fasted for 24 h before starting all experiments, and then animals were orally administrated with test drugs (DA-9701, or conventional prokinetics as positive controls at the indicated doses) or 3% (w/v) HPMC as a vehicle. The efficacious dosages of positive controls used in all experiments of this study were chosen based on literatures previously reported (Yoshida et al., 1989; Iwanaga et al., 1991; Yoshida et al., 1993; Iwanaga et al., 1996).

Gastric emptying

Gastric emptying was measured according to the method of Ozaki and Sukamoto (1999) with some modifications. (i) Normal rats were given 2 ml of semisolid meals by gavages at 45 min after drug administration. Following 35 min animals were sacrificed, and

the weights of stomachs and contents in the stomachs were measured to determine gastric emptying. Gastric emptying (%) = [1−weight of test stomach/weight of 0 time control stomach] × 100. (ii) Animals were given 2 ml of semisolid meal at 45 min after drug administration, and simultaneously injected with apomorphine (s.c., 0.05 mg/kg). Following 50 min, gastric emptying was determined by the same method described above. (iii) Animals were given 2 ml of liquid meal containing 0.05% phenol red at 60 min after drug administration, and simultaneously injected with cisplatin (i.p., 10 mg/kg). Following 20 min the amount of phenol red remaining in the stomachs was measured according to the method of Yoshida et al. (1989). Gastric emptying (%) = [1−OD 560 nm of test stomach/OD of 0 time control stomach] × 100 [0 time control] was determined.

Gastrointestinal transit

Gastrointestinal transit was measured using the method of Kalff et al. (1999) with some modification. (i) Animals ($n = 6$/each group) were given a test meal (FITC-dextran) by gavages at 60 min after drug administration. Following 15 min animals were sacrificed. The small intestinal portion was carefully removed and divided into 10 equal segments. The FITC-dextran concentration in each segment was measured using a microplate reader (POLARstar OPTIMA, BMG Labtech), expressed as a fraction of total tracer recovered, and presented as the mean geometric center (MGC) of distribution. (ii) For inducing delayed intestinal transit laparotomies 3 cm long in the median abdomen were performed and closed immediately. Following 4 h, animals were orally administrated with test drugs, and MGC was determined as the same method described above. (iii) When animals ($n = 6$/each group) were administrated with test drugs atropine was simultaneously injected (i.p., 1 mg/kg). MGC was determined as the same method described above.

Gastric accommodation

The effect on gastric accommodation was examined according to the method of De Ponti et al. (2003) with some modification. The five female Beagle dogs (7–9 kg) were operated on under general Tiletamine/Zolazepam (Zoletil, Virbac Laboratories) anesthesia (i.v., 10 mg/kg). Through a midline laparotomy a gastric cannula was inserted into the stomach, and exteriorized in the anterior aspect of the abdomen. The experiments were performed on conscious dogs after complete recovery following surgery. Animals were administrated with test drugs, and after an equilibration period intrabag pressure was increased with 2-mmHg increments every 3 min, starting from the minimal distending pressure up to 16 mmHg without deflating the barostat bag at each pressure step. Changes in intragastric volume occurring after administration of DA-9701 or cisapride were automatically measured at the peak of the response. In each experiment, three pressure–volume curves were obtained, allowing a 50-min interval between the ends of a distention cycle and beginning of the subsequent cycle. In each dog, we carried out three sets of experiments, performing each experiment in duplicate.

Data analysis

Results were expressed as mean ± SEM. Differences in the data were evaluated by Student's t-test. p values < 0.05 were considered as a significant difference between two groups.

Results

Effects of DA-9701 on gastric emptying

In normal rats, DA-9701 significantly accelerated gastric emptying compared to the control group. As shown in Fig. 1A, the control group indicated that only 23.7 ± 3.5% were emptied, but decrease in residual meal by DA-9701 was significant. The effects were dose dependent in the range of doses from 0.03 to 3 mg/kg (except 1 mg/kg), and at two peak points residual percentage of the meal was 40.2 ± 3.7% (0.3 mg/kg, $p < 0.01$) and 41.0 ± 1.9% (3 mg/kg, $p < 0.01$) and the effects were comparable to that of mosapride of 10 mg/kg. Neither itopride at a dose of 30 mg/kg nor domperidone at a dose of 10 mg/kg could significantly increase the gastric emptying. Next, we harbored the delayed models of gastric emptying to assess whether DA-9701 is capable of correcting abnormally depressed gastric emptying. When apomorphine (s.c., 0.05 mg/kg) was administrated, gastric emptying of a semisolid meal was markedly delayed to approximately 60% compared with normal rats (18.9 ± 4.3% vs. 48.9 ± 7.3%). The delayed gastric emptying was restored by DA-9701 from the dose of 0.3 mg/kg, and the maximal effect was shown in the rats treated with 3 mg/kg (Fig. 1B), which was superior to that of mosapride (10 mg/kg). In the other delayed model, cisplatin (i.p., 10 mg/kg) greatly delayed gastric emptying of liquid meals to a level half that of normal. DA-9701 at a dose of 3 mg/kg significantly restored delayed gastric emptying to an almost normal level (Fig. 1C). These results suggested that DA-9701 could accelerate gastric emptying in normal conditions, and furthermore that they could correct the apomorphine- and cisplatin-induced abnormally delayed gastric emptying.

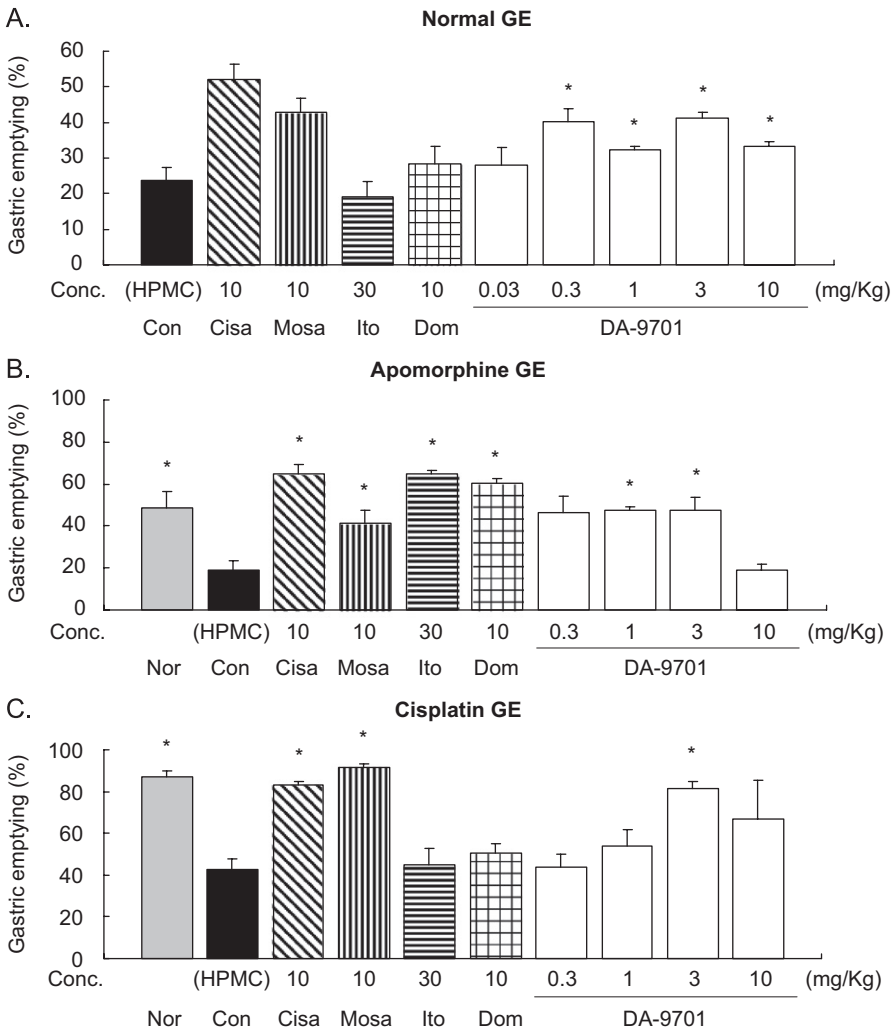


Fig. 1. Effects of DA-9701 on gastric emptying. After 24 h fasting, the animals ($n = 6$/each group) were orally administrated with DA-9701 at indicated dosages (□), cisapride (▨, 10 mg/kg), mosapride (▥, 10 mg/kg), itopiride (▤, 30 mg/kg), and domperidone (▦, 10 mg/kg) or 3% HPMC as vehicle (■, control). (A) Gastric emptying in normal rats, (B) in apomorphine-induced delay model, and (C) in cisplatin-induced delay model. % gastric emptying was calculated as described in Materials and methods. Values are the mean ± SEM of 6–7 experiments. *$p < 0.05$ vs. control (Student's t-test).

Effects of DA-9701 on gastrointestinal transit

In normal rats, as shown in Fig. 2A, the positive controls including cisapride, mosapride, itopride, and domperidone at their biologically efficacious dosages were not able to significantly increase the transit distances of FITC-dextran compared with the control, however, DA-9701 caused FITC-dextran to travel a significantly longer distance than the control, MGC was increased by 5.02 ± 0.13 ($p < 0.05$) when treated with 10 mg/kg. Next, we harbored the delayed models of gastrointestinal transit to assess whether DA-9701 is capable of restoring abnormally suppressed gastrointestinal transit. DA-9701 normalized laparotomy induced delayed gastrointestinal transit is presented in Fig. 2B. The MGC was greatly diminished by 2.85 ± 0.12 in rats after operation; however, DA-9701 considerably increased the MGC from the dose of 3 mg/kg, those were 3.19 ± 0.02 and 3.20 ± 0.08 at 3 and 10 mg/kg, respectively, which were comparable to that shown in mosapride. Furthermore, in other delay model using atropine, high dosages of atropine (i.p., 1 mg/kg) greatly decreased the geometric center up to 3.32 ± 0.16 compared with normal rats (4.04 ± 0.10). DA-9701 significantly raised the MGC, indicating acceleration in gastrointestinal transit. The maximum effect was presented at the dose of 1 mg/kg, and the MGC was 4.09 ± 0.22 (Fig. 2C). In contrast, in this model, conventional prokinetics were not able to normalize atropine-induced delay in GI transit. These results suggested that DA-9701 could accelerate gastrointestinal transit in normal conditions, and restored

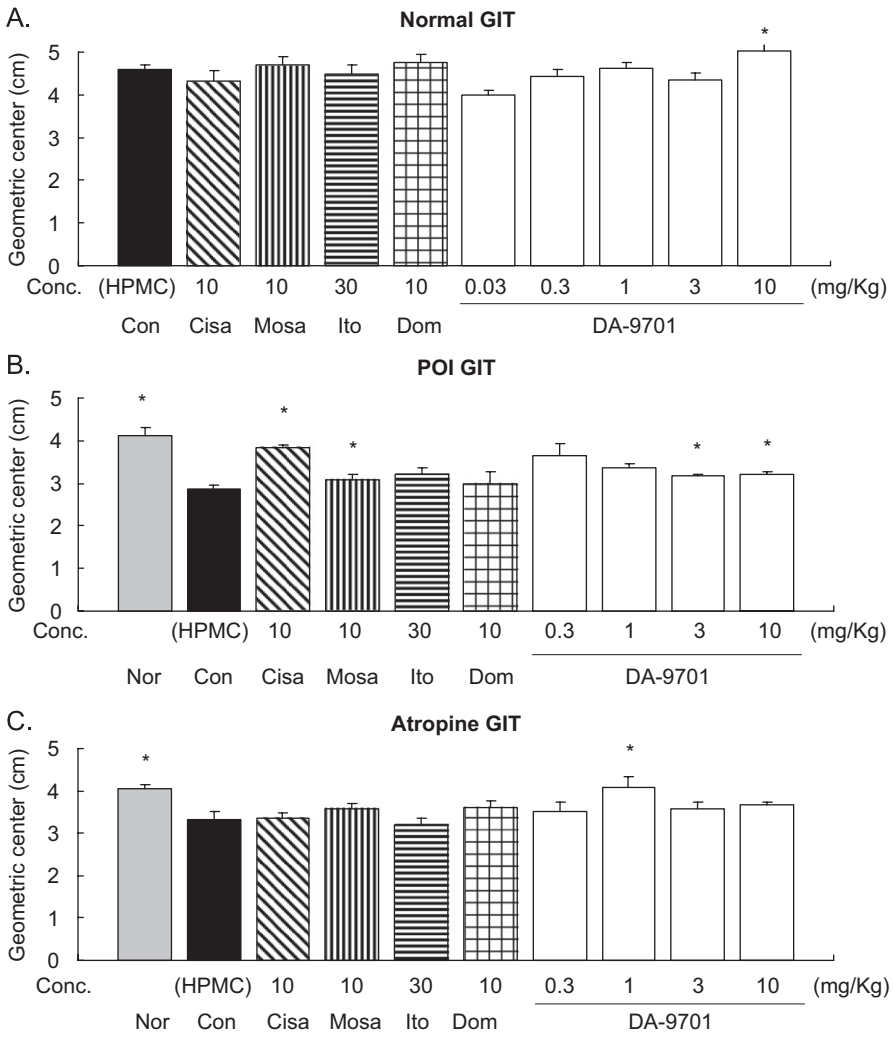


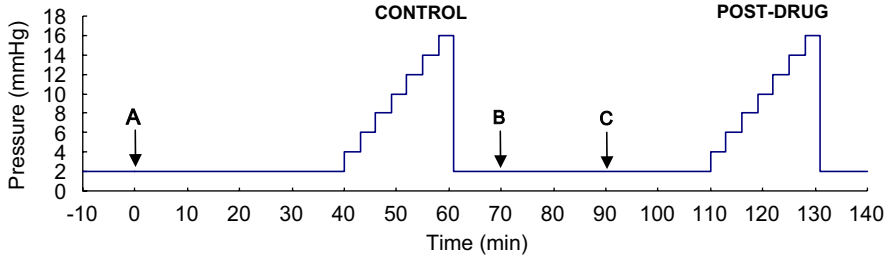
Fig. 2. Effects of DA-9701 on gastrointestinal transit. After 24 h fasting the animals ($n = 6$/each group) were orally administrated with DA-9701 at indicated dosages (□), cisapride (▨, 10 mg/kg), mosapride (▥, 10 mg/kg), itopiride (▤, 30 mg/kg), and domperidone (▦, 10 mg/kg) or 3% HPMC as vehicle (■, control). (A) Gastrointestinal transit in normal rats, (B) in laparotomy-induced delay model, and (C) in atropine-induced delay model. MGC was calculated as described in Materials and methods. Values are the mean ± SEM of 6–7 experiments. *$p < 0.05$ vs. control (Student's t-test).

laparotomy and atropine-induced delay in gastrointestinal transit.

Effects of DA-9701 on gastric accommodation

Effects of DA-9701 on gastric accommodation were assessed using a barostat in Beagle dogs. The first distension cycle was used to unfold the intragastric bag, and the values recorded were discarded. The next distension cycle was used as a control. For the third distention cycle DA-9701 or cisapride was used (Fig. 3A). As it was found that it takes 40 min for DA-9701 to present its effects, bolus of DA-9701 was gavaged 40 min before starting the third distension cycle. Baseline gastric volumes measured at 2 mmHg were 5 ± 4 ml and 11 ± 6 ml before and after DA-9701 treatment, respectively (Fig. 3B). DA-9701 (0.3 mg/kg) induced a relaxation of the proximal stomach. With the use of the exponential regression analysis, a significant shift of the pressure–volume curve was observed by DA-9701 compared with the control, resulting in great increase in the slope at $_{1/2}P_{max}$ by 21 ± 5.9 ml (vs. 14.5 ± 4.5, $p < 0.05$), and the volume at $_{1/2}P_{max}$ by 66 ± 27 ml (vs. 40 ± 18, $p < 0.05$) (Fig. 3B). There were significant differences in the volumes between DA-9701 and control group at the pressure of 10 and 12 mmHg (Fig. 3C). Cisapride was injected intravenously 20 min before starting the third distention cycle. A significant shift of pressure–volume curve was observed with 0.3 mg/kg of cisapride. The slope at $_{1/2}P_{max}$ was 23 ± 10.4 (vs. 19.6 ± 7.6, $p < 0.05$) and the

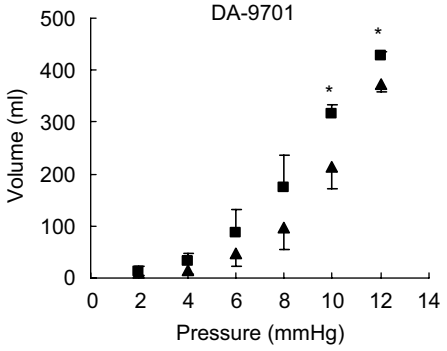
A.



B.

	Exponential Model				
	r^2	V_o, ml	K_1, $mmHg^{-1}$	Slope at ½P_{max}, ml/mmHg	Vol at ½P_{max}, ml/mmHg
Control	0.9917	5 ± 4	0.45 ± 0.07	14.5 ± 4.5	40 ± 18
DA-9701 (0.3)	0.9714	11 ± 6	0.43 ± 0.09	21.0 ± 5.9*	66 ± 27*
Control	0.9269	9 ± 7	0.38 ± 0.09	19.6 ± 7.6*	59 ± 33*
Cisapride (0.3)	0.7201	13 ± 12	0.38 ± 0.11	23.0 ± 10.4	76 ± 50

C.



D.

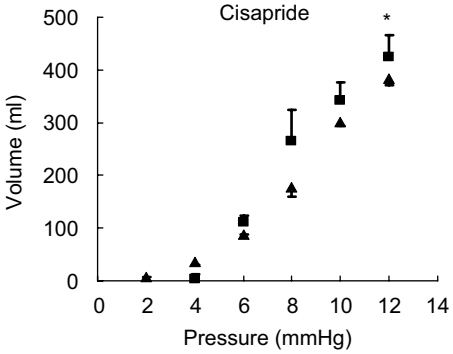


Fig. 3. Effects of DA-9701 on gastric accommodation in Beagle dogs (A) Experimental procedure described in Materials and methods. A, vehicle, 3% HPMC; B, administration of DA-9701 (bolus injection, p.o., 0.3 mg/kg); or C, administration of cisapride (i.v., 0.3 mg/kg). (B) Parameters calculated for the volume–pressure relationship in vehicle and after DA-9701 or cisapride administrations. (C) Pressure–volume relationship in the canine proximal stomach in DA-9701 treated (■) and vehicle group (▲). (D) Pressure–volume relationship in the canine proximal stomach in cisapride (■) and vehicle group (▲). Values are the mean ± SEM of 6–7 experiments. *$p < 0.05$ vs. control (Student's t-test).

volume at $_{1/2}P_{max}$ was 76 ± 50 ml ($p < 0.05$), while it was 59 ± 33 ml in the control (Fig. 3B). There was significant difference in the volume at the pressure of 12 mmHg (Fig. 3D). These results suggested that DA-9701 could induce the gastric relaxation and increase gastric compliance.

Discussion

Given the heterogeneity of FD it appears natural that there is no single available therapy sufficiently capable of providing relief to the majority of FD patients. With effects of similar or greater magnitude to conventional prokinetics and encouraging safety profile several herbal medicinal products have been assessed as to their feasibilities for the treatment of FD (Thompson Coon and Ernst, 2002). For example, a Japanese herbal medicine containing three herbs, Dai–Kenchu–To, has been reported to enhance not only upper GI motility through cholinergic receptor (Jin et al., 2001) but also GI transit in delayed models induced by laparotomy or morphine (Nakamura et al., 2002; Fukuda et al., 2006). Dai–Kenchu–To is frequently applying for patients with GI disorder and post-operative ileum in Japan. Liu–Jun–Zi–Tang (also known as TJ-43) consisting of six herbs has been reported to increase gastric emptying and promote gastric adaptive relaxation (Hayakawa et al., 1999), which has been identified as an effective treatment for dyspeptic symptoms (Tatsuta and Iishi, 1993).

In addition, the clinical trial for several herbal products including peppermint oil and caraway oil in the treatment of FD resulted in greater reduction in gastrointestinal symptom score (Saad and Chey, 2006).

For the first time, we revealed that DA-9701, an extract from Pharbitis Semen and Corydalis Tuber, has promising effects on GI motor functions, which include accelerating gastric emptying and meal transit as well as enhancing gastric accommodation. It was founded that DA-9701 enhanced the gastric emptying in normal rats, and the effective dose was 0.3 mg/kg, which was much lower than those of conventional prokinetics. Apomorphine has inhibitory effects on gastric emptying by acting as a dopamine agonist (Blancquaert et al., 1982), and it is well known that cisplatin, an antineoplastic agent causes severe side effects on GI function such as delay in gastric emptying as well as nausea and vomiting (Eeckhout and Vedder, 1988). DA-9701 could abolish the delayed gastric emptying induced by apomorphine and cisplatin. In addition, the gastrointestinal transit of meal was accelerated by DA-9701 at the dose of 10 mg/kg in normal rats, while currently prescribing drugs rarely enhanced the gastrointestinal transit in our experimental system. Delayed GI transit by laparotomy was significantly restored by the treatment with DA-9701, and atropine-induced delayed GI transit was also abolished by DA-9701 at the dose of 1 mg/kg. Based on these results we understand that DA-9701 might be much superior to conventional therapeutics particularly for gastrointestinal transit both in normal as well as in abnormal conditions. Furthermore, DA-9701 efficiently increased gastric volume according to the increments in pressure similar to that extension shown in cisapride. In addition, repeated dose toxicity testing revealed that DA-9701 has no toxic effects at all using much higher doses than an effective dose, and showed no prolongation of the electrocardiographic QT intervals, which is a side effect shown in cisapride (Kii et al., 2001), even at the dose of 1 g/kg in rats. Finally preliminary data from a small-scale randomized and placebo-controlled clinical trial for 64 FD patients suggested DA-9701 significantly reduced the gastrointestinal symptoms compared to the placebo-treated patients (data not shown). Identification of the active compound(s) responsible for the gastroprokinetic effects of DA-9701 is to be remained. Several biologically active compounds including alkaloids, diterpenes, and resin glycosides (Yokota et al., 1970; Matsuda et al., 1988; Kubo et al., 1994; The Editing Commission of the Textbook Pharmacognosy, 2006) in two herbs consisting of DA-9701 have been identified and characterized, however no compound(s) from DA-9701 were reported to show the effects propelling the movement of GI tract. To find active compound(s) for prokinetic effects of DA-9701, we are currently conducting the binding assays for various neurotransmitter receptors and organ bath experiments using activity-guided fractionation and purification of isolated components. Taken together, all our data indicated that DA-9701 might have great potential as a safe and effective prokinetic agent capable of lessening gastrointestinal symptoms and increasing quality of life in FD patients. Considering safety and pharmacological effects of DA-9701 on GI, further studies are definitely warranted to prove the clinical value through highly qualified and controlled clinical trials.

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