

## Effect of DA-9701 on gastric emptying in a mouse model: Assessment by <sup>13</sup>C-octanoic acid breath test

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### Abstract

**AIM:** To evaluate the effects of DA-9701 on the gastric emptying of a solid meal using the <sup>13</sup>C-octanoic acid breath test in a mouse model.

**METHODS:** Male C57BL/6 mice aged > 8 wk and with body weights of 20-25 g were used in this study. The solid test meal consisted of 200 mg of egg yolk labeled with 1.5 L/g <sup>13</sup>C-octanoic acid. The mice were placed in a 130 mL chamber flushed with air at a flow speed of 200 mL/min. Breath samples were collected for 6 h. The half-emptying time and lag phase were calculated using a modified power exponential model. To assess the reproducibility of the <sup>13</sup>C-octanoic acid breath test, the breath test was performed two times at intervals of one week in ten mice without drug treatment. To assess the gastrokinetic effects of DA-9701, the breath

test was performed three times in another twelve mice, with a randomized crossover sequence of three drug treatments: DA-9701 3 mg/kg, erythromycin 6 mg/kg, or saline. Each breath test was performed at an interval of one week.

**RESULTS:** Repeatedly measured half gastric emptying time of ten mice without drug treatment showed 0.856 of the intraclass correlation coefficient for the half gastric emptying time ( $P = 0.004$ ). The mean cumulative excretion curve for the <sup>13</sup>C-octanoic acid breath test showed accelerated gastric emptying after DA-9701 treatment compared with the saline control ( $P = 0.028$ ). The median half gastric emptying time after the DA-9701 treatment was significantly shorter than after the saline treatment [122.4 min (109.0-137.9 min) vs 134.5 min (128.4-167.0 min), respectively;  $P = 0.028$ ] and similar to that after the erythromycin treatment [123.3 min (112.9-138.2 min)]. The lag phase, which was defined as the period taken to empty 15% of a meal, was significantly shorter after the DA-9701 treatment than after the saline treatment [48.1 min (44.6-57.1 min) vs 52.6 min (49.45-57.4 min), respectively;  $P = 0.049$ ].

**CONCLUSION:** The novel prokinetic agent DA-9701 accelerated gastric emptying, assessed with repeated measurements in the same mouse using the <sup>13</sup>C-octanoic acid breath test. Our findings suggest that DA-9701 has therapeutic potential for the treatment of functional dyspepsia.

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**Key words:** DA-9701; Gastric emptying; Prokinetic agent; Breath test; Functional dyspepsia

**Core tip:** DA-9701 is a newly formulated prokinetic agent obtained from extracts of Pharbitis Semen and Corydalis Tuber. The <sup>13</sup>C-octanoic acid breath test is a reliable and responsive method for measuring gastric

emptying in small laboratory animal. This technique can be performed repeatedly in the same animal and reflect exact pharmacological effects without sacrifice of the animal. This study demonstrated the gastrokinetic effects of DA-9701, using repeated  $^{13}\text{C}$ -octanoic acid breath tests in the same animal. The gastrokinetic effect of DA-9701 could have therapeutic potential for the treatment of familial dysautonomia.

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## INTRODUCTION

DA-9701 is a newly formulated prokinetic agent obtained from extracts of *Pharbitis Semen* and *Corydalis Tuber*. Both the seed of *Pharbitis Semen* and the root of *Corydalis Tuber* have been used in traditional Oriental medicine for the treatment of gastrointestinal symptoms. DA-9701 and its components accelerated gastric emptying and improved gastric accommodation in animal model<sup>[1-4]</sup>. A previous study demonstrated the gastrokinetic effect of DA-9701 in a rat model<sup>[1]</sup>, using the method of Ozaki *et al.*<sup>[5]</sup>. With this model, the animal must be killed to assess gastric emptying, and consequently, gastric emptying can only be measured at that one point in time. The disadvantage of this method is that it is impossible to assess gastric emptying repeatedly in the same animal. Therefore, the utility of the model is limited for evaluating pharmacologically induced gastric emptying because there is great intersubject variability.

Stable isotope breath tests are indirect noninvasive tests for measuring gastric emptying. Their advantages include the absence of a radiation hazard, ease of handling, and no requirement for positioning, unlike scintigraphic tests<sup>[6]</sup>. Breath tests offer an attractive method of measuring gastric emptying in small laboratory animals because the animal need not be killed, thus allowing repeated measurements to be made in the same animal. With the  $^{13}\text{C}$ -octanoic acid breath test, gastric emptying can be assessed noninvasively, and the differences in gastric emptying induced in small laboratory animals by pharmacological agents can be quantified<sup>[7-11]</sup>. This test is a useful tool in the development of new prokinetic agents that modulate gastric emptying. The aim of this study was to evaluate the effects of DA-9701 on the gastric emptying of a solid meal using the  $^{13}\text{C}$ -octanoic acid breath test in a mouse model.

## MATERIALS AND METHODS

### Animals

Male C57BL/6 mice, aged > 8 wk and with body weights

of 20-25 g, were used for the breath test. Ten mice were used to assess the reproducibility of the  $^{13}\text{C}$ -octanoic acid breath test and another 12 mice were used to evaluate the effects of DA-9701. Sample sizes were calculated from the equation below by referring to a previous study using C57BL/6 mice<sup>[8]</sup>:  $n = 2 + C (s/d)^2$ , where  $s$  is SD,  $d$  is expected difference between two means, and  $C$  is constant. A sample size of 12 mice was suitable to identify, with a power of 0.8, the expected difference in half gastric emptying time of 50 min with an alpha significance level of 0.05. All the mice were housed in a room maintained at 21 °C-23 °C on a 14/10 h light/dark cycle. The mice had continuous access to water and a standard commercial diet. All experiments were approved by the Institutional Animal Care and Use Committee of the Catholic University of Korea, Seoul, South Korea.

### Test meal

The gastric emptying rates were assessed for a solid egg yolk meal.  $^{13}\text{C}$ -Octanoic acid (Octanoic acid-1- $^{13}\text{C}$ , 99 atom %  $^{13}\text{C}$ , Sigma-Aldrich Co. LLC, St Louis, Missouri, United States) was added to raw yolk at a concentration of 1.5  $\mu\text{L/g}$ . The yolk was homogenized and heated in water at 60 °C for 120 min. The test meal (200 mg) was given to each animal after an overnight fast with free access to water and was completely consumed by the mouse within 1 min in the breath test chamber.

### Breath test protocol

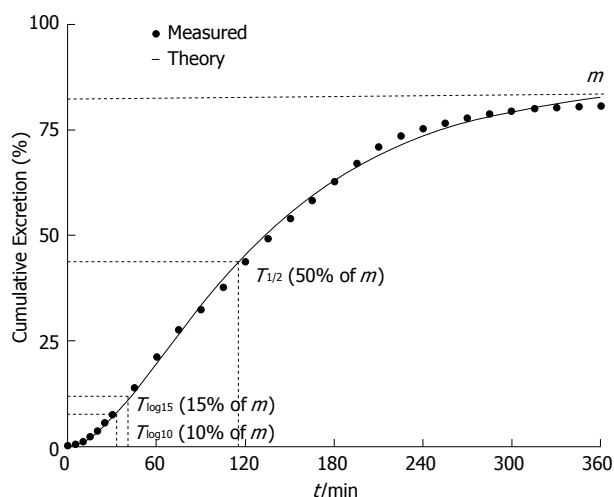
To assess the gastric emptying rate using the  $^{13}\text{C}$ -octanoic acid breath test with measurements made up to 360 min, the mice were fasted overnight<sup>[7,8]</sup>. They were then placed in a 130 mL gas-tight rubber-sealed chamber with room air. The flow rate of air was 200 mL/min, which was selected because this rate was sufficient to flush any residual  $\text{CO}_2$  from the chamber between the sampling time points. Three-way valves were connected to the chamber for air inlet and outlet to allow sampling. To collect a breath sample, the airflow through the chamber was stopped for 4 min. At the end of the breath-accumulation period, 10 mL of breath was syringed from the chamber, and the airflow through the chamber was restored. Each mouse was maintained in the chamber for the whole 360 min sampling procedure. A baseline breath sample was taken before the test meal was consumed. Further breath samples were collected at 5 min intervals for the first 30 min, and at 15 min intervals thereafter until 360 min after the consumption of the test meal.

### Reproducibility of the breath test

To assess the reproducibility of the  $^{13}\text{C}$ -octanoic acid breath test, the breath test was performed two times at intervals of 1 wk in ten mice without drug treatment.

### Drug treatment

This study was designed as a randomized crossover study. DA-9701 (3 mg/kg) was the test drug, erythromycin (6 mg/kg) the positive control, and normal saline the

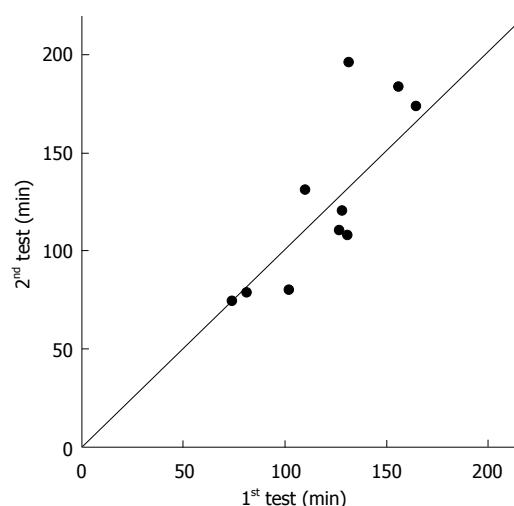


**Figure 1** Typical excretion curve of the  $^{13}\text{C}$ -octanoic acid breath test in the mouse model.  $m$ : The total cumulative  $^{13}\text{C}$  recovery when time is infinite;  $T_{1/2}$ : Half gastric emptying time;  $T_{\text{lag}10}$ : Lag phase of 10 % emptying;  $T_{\text{lag}15}$ : Lag phase for 15% emptying.

placebo. There were six possible permutations of the drug treatment sequences, and two animals were allocated to each permutation. The test drug and the positive control were suspended in distilled water for their oral administration. A 10 mL/kg volume of DA-9701, erythromycin, or saline was given orally to each mouse by gavage 1 h before the breath test. The breath test was performed three times in each animal at intervals of 1 wk.

### Data analysis

The  $^{13}\text{CO}_2$  content of each breath sample was analyzed using a HeliView isotope ratio mass spectrometer (Medi-chems, Seoul, South Korea). The  $[\text{C}^{13}]/[\text{C}^{12}]$  ratio ( $\delta$ ) was expressed as parts per thousand relative to the Pee Dee Belemnite calcium carbonate international primary standard. The gastric emptying rates were calculated from the resultant  $^{13}\text{CO}_2$  excretion curves. The  $\text{CO}_2$  production rate of the mice was assumed to be 40 mL/kg per minute based on normal values for the resting metabolic parameters measured in C57BL/6 mice<sup>[12]</sup>. The percentage  $^{13}\text{CO}_2$  cumulative values were fitted using a modified power exponential model<sup>[13]</sup>:  $y = m(1 - e^{-kt})^\beta$ , where  $y$  is the cumulative percentage of  $^{13}\text{CO}_2$  excretion in breath at time  $t$  (h), and  $m$ ,  $k$ , and  $\beta$  are estimated parameters. In this model,  $m$  is interpreted as the total cumulative  $^{13}\text{C}$  recovery when the time is infinite. The cumulative  $^{13}\text{CO}_2$  excretion cannot reach 100% because a substantial amount of the orally administered dose is fixed in the bicarbonate pool in the body. Because the cumulative excretion reaches a steady state, sampling up to 360 min allows the calculation of  $m$ , the theoretical recovery after infinite time. The half gastric emptying time ( $T_{1/2}$ ), the lag phase for 10% emptying ( $T_{\text{lag}10}$ ), and the lag phase for 15% emptying ( $T_{\text{lag}15}$ ) in the breath test were calculated from this model as  $T_{1/2} = (-1/k) \times \ln[1 - (0.5^{1/\beta})]$ ;  $T_{\text{lag}10} = (-1/k) \times \ln[1 - (0.1^{1/\beta})]$ ;  $T_{\text{lag}15} = (-1/k) \times \ln[1 - (0.15^{1/\beta})]$ .



**Figure 2** Reproducibility of the  $^{13}\text{C}$ -octanoic acid breath test in ten mice.

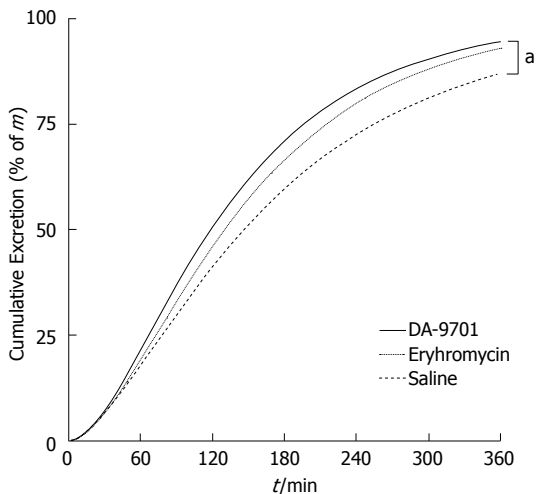
### Statistical analysis

The results are expressed as medians and interquartile ranges. The reproducibility of breath test was evaluated using the intraclass correlation coefficient. A repeated measurements ANOVA followed by post hoc test at the point of every 60 min was performed for comparison of total cumulative excretion curve after drug treatment. Differences in the data were evaluated using the Wilcoxon signed-rank test for comparisons of the half gastric emptying times and lag phases after drug treatment. A difference was considered significant when the  $P$  value was less than 0.05.

## RESULTS

A typical excretion curve for  $^{13}\text{C}$ -octanoic acid breath test of a mouse is presented in Figure 1. Repeatedly measured half gastric emptying time of ten mice is presented in Figure 2. The half gastric emptying times of the first and second breath tests were 127.5 min (96.7–137.6 min) and 115.4 (79.9–176.4 min). The half gastric emptying times of the first and second breath tests showed good correlation (intraclass correlation coefficient = 0.856,  $P = 0.004$ ). The effects of the drug treatments on gastric emptying are shown in Figure 3. The cumulative excretion curve for  $^{13}\text{C}$ -octanoic acid breath showed accelerated gastric emptying after treatment with DA-9701 compared with that after treatment with saline ( $P = 0.028$ ). The effect of DA-9701 treatment on gastric emptying was similar to that of erythromycin.

The half gastric emptying times and lag phases are presented in Table 1. Both DA-9701 and erythromycin treatments induced significantly shorter half gastric emptying times compared with that induced with saline ( $P = 0.028$  and  $P = 0.049$ , respectively). There was no significant difference in the half gastric emptying times of the DA-9701- and erythromycin-treated mice. There was no significant difference in  $T_{\text{lag}10}$  among the treatments.  $T_{\text{lag}15}$  was significantly shorter in mice treated with DA-9701



**Figure 3** Mean excretion curve of the  $^{13}\text{C}$ -octanoic acid breath test in mice treated with DA-9701, erythromycin, and saline. m: The total cumulative  $^{13}\text{C}$  recovery when time is infinite.  $^aP < 0.05$  between DA-9701 and saline.

**Table 1** Half gastric emptying time and lag phase measured by the  $^{13}\text{C}$ -octanoic acid breath test in the mice treated with DA-9701, erythromycin, and saline

	DA-9701 (n = 12)	Erythromycin (n = 12)	Saline (n = 12)
$T_{1/2}$ (min)	122.4 (109.0-137.9) <sup>1</sup>	123.3 (112.9-138.2) <sup>2</sup>	134.5 (128.4-167.0)
$T_{\text{lag}10}$ (min)	38.5 (33.2-46.4)	37.9 (35.8-41.4)	39.5 (35.2-45.3)
$T_{\text{lag}15}$ (min)	48.1 (44.6-58.5) <sup>2</sup>	49.3 (46.5-53.3)	52.6 (48.9-57.6)

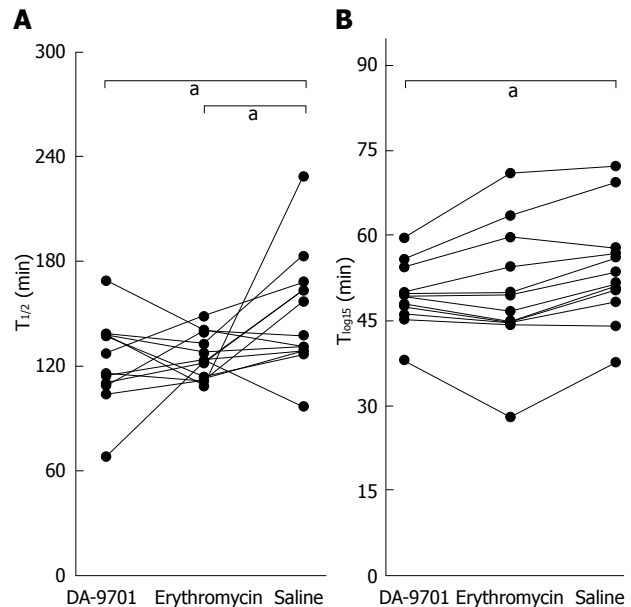
Data represent median with interquartile range in parentheses. <sup>1</sup> $P = 0.028$ , <sup>2</sup> $P = 0.049$  vs saline treatment (Wilcoxon's signed ranks test).  $T_{1/2}$ : Half gastric emptying time;  $T_{\text{lag}10}$ : Lag phase for 10 % emptying;  $T_{\text{lag}15}$ : Lag phase for 15% emptying.

than in mice treated with saline ( $P = 0.049$ ). The half gastric emptying time and  $T_{\text{lag}15}$  for each mouse treated with saline, DA-9701, or erythromycin is presented in Figure 4.

## DISCUSSION

Dyspeptic symptoms are common problem in primary health care and gastroenterology practice. Although the precise pathophysiology of functional dyspepsia (FD) is not fully understood, disturbed gastric emptying is one of the important abnormalities in FD patients<sup>[14,15]</sup>. Current treatment approaches to FD include gastric acid suppression and gastroprokinetic drugs as primary treatment options<sup>[16]</sup>. However, no satisfactory therapeutic approach is currently available in clinical practice. There is an increasing need for the development of safe and effective prokinetic drugs without adverse effects<sup>[17-19]</sup>.

We have demonstrated the effects of DA-9701 on gastric emptying, using repeated  $^{13}\text{C}$ -octanoic acid breath tests in the same animal. DA-9701 shortened both the half emptying time and the lag phase, and these effects were similar to those of erythromycin. The half gastric emptying times achieved with the placebo and erythromycin in our model were similar to those reported in previous studies that



**Figure 4** Half gastric emptying time and lag phase for 15% emptying measured by the  $^{13}\text{C}$ -octanoic acid breath test in the each mouse treated with DA-9701, erythromycin, and saline. A: Half gastric emptying time ( $T_{1/2}$ ); B: Lag phase for 15% emptying ( $T_{\text{lag}15}$ ).  $^aP < 0.05$  vs saline.

used the same breath test<sup>[8]</sup>. We selected a dose of 3 mg/kg DA-9701 based on a previous study of the appropriate DA-9701 doses in a rat model, which showed dose-dependent effects in the range from 0.03 to 3 mg/kg<sup>[1]</sup>. Another experiment in which DA-9701 was administered at 3 mg/kg also showed accelerated gastric emptying in a model of delayed gastric emptying induced with apomorphine and cisplatin. DA-9701 and its components (corydaline and tetrahydroberberine) accelerated gastric emptying in a rat model when a method that requires the animals to be killed was used, although comparisons within the same animal were impossible<sup>[1-3]</sup>. We performed the repeated breath tests in each mouse after treatment with either DA-9701, the positive control, or the placebo, according to all possible permutations of the drug treatment sequence, and identified the prokinetic effects of DA-9701.

DA-9701 is a newly formulated prokinetic agent obtained from extracts of *Pharbitis Semen* and *Corydalis Tuber*. Both the seed of *Pharbitis Semen* and the root of *Corydalis Tuber* have been used in traditional Oriental medicine for the treatment of gastrointestinal symptoms. As well as accelerating gastric emptying, DA-9701 and its components improved gastric accommodation in a dog model with a barostat<sup>[1-4]</sup>. DA-9701 is composed of several isoquinoline alkaloid compounds, including corydaline, berberine, protopine, and palmatine<sup>[20-23]</sup>. Although the exact mechanism of its action has not been identified, tetrahydroberberine from DA-9701 has the properties of a  $\text{D}_2$  receptor antagonist and a  $5\text{-HT}_{1A}$  receptor agonist, with micromolar affinities for the dopamine  $\text{D}_2$  and  $5\text{-HT}_{1A}$  receptors<sup>[2]</sup>. DA-9701 significantly improved the symptoms of patients with FD, with efficacy similar to that of itopride and a comparable safety profile<sup>[24]</sup>.

In this study, we have demonstrated the gastrokinetic



effect of DA-9701 using the  $^{13}\text{C}$ -octanoic acid breath test in mice. A variety of techniques have been used to assess gastric emptying in small laboratory animals. Most techniques require the animal to be killed and the contents of the stomach and intestine to be quantified by measuring their radioactivity, counting the glass beads remaining, or measuring the concentration of a marker. The  $^{13}\text{C}$ -octanoic acid breath test has been reported to be a reliable and responsive method for measuring gastric emptying in small laboratory animal<sup>[7,8,10,25]</sup>, and has several advantages over other techniques. First, it allows repeated measurements to be made in the same animal, allowing exact pharmacological effects to be identified and minimizing the number of animals killed. Second, it does not require the animals to be handled or restrained, in contrast to scintigraphic tests. The results can also be expressed as rate curves and cumulative excretion curves. Therefore, the breath test can be used to determine the effects of physiological or pharmacological interventions on gastrointestinal motility, especially in developmental programs for new prokinetic drugs. However, to measure gastric emptying, the breath test requires a relatively long time and considerable effort to sample the animals' breath.

In conclusion, DA-9701 accelerates gastric emptying, and its effect is similar to that of erythromycin. The  $^{13}\text{C}$ -octanoic acid breath test can be a useful tool to reflect physiological or pharmacological effects on gastric motility, especially in developmental programs for new prokinetic drugs. The gastrokinetic effect of DA-9701 could have therapeutic potential for the treatment of FD.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Dyspeptic symptoms are common problem in primary health care and gastroenterology practice. Disturbed gastric emptying is one of the important abnormalities in functional dyspepsia (FD) patients. Gastroprokinetic drugs in one of the primary treatment options. There is an increasing need for the development of safe and effective prokinetic drugs without adverse effects

### Innovations and breakthroughs

A previous study demonstrated the gastrokinetic effect of DA-9701 in a rat model using the method of Ozaki and Sukamoto. With this model, the animal must be killed to assess gastric emptying, and consequently, gastric emptying can only be measured at that one point in time. The disadvantage of this method is that it is impossible to assess gastric emptying repeatedly in the same animal. This study demonstrated the gastrokinetic effect of DA-9701 using repeated the  $^{13}\text{C}$ -octanoic acid breath test in same animal with minimizing the number of animals killed.

### Applications

The gastrokinetic effect of DA-9701 could have therapeutic potential for the treatment of FD. The  $^{13}\text{C}$ -octanoic acid breath test can be a useful tool to reflect physiological or pharmacological effects on gastric motility, especially in developmental programs for new prokinetic drugs.

## Terminology

$^{13}\text{C}$ -octanoic acid breath test is one of stable isotope breath tests for measuring gastric emptying. The test meal containing  $^{13}\text{C}$ -labelled substrates is retained in the stomach and emptied into the duodenum. The  $^{13}\text{C}$ -labelled substrates are rapidly absorbed and transported to the liver. They are oxidized to  $^{13}\text{CO}_2$  in the liver and excreted in the breath. Gastric emptying is the rate-limiting step that makes it possible to use the rate of  $^{13}\text{CO}_2$  appearance in the breath approximate to the gastric emptying rate.

## Peer review

This study examines the effects of DA-9701, a novel phyto-derived prokinetic agent, on gastric emptying of normal C57BL/6 mice. The authors used  $^{13}\text{C}$ -octanoic acid breath test to investigate gastric emptying of three treatments (DA-9701, erythromycin vs saline, the latter used as placebo) with a randomized crossover design. This study is interesting and original in its methodological part because it presents a novel method to assess gastric emptying over time rather than evaluating a single moment after sacrificing laboratory animals. The authors precisely describe their experiments using the breath test technique, including a power calculation. Compared to saline, DA-9701 evoked a more rapid emptying similarly to erythromycin. The finding of a prokinetic effect of DA-9701 on gastric emptying is very promising in view of potential therapeutic options in FD.

## REFERENCES

- 1 Lee TH, Choi JJ, Kim DH, Choi S, Lee KR, Son M, Jin M. Gastroprokinetic effects of DA-9701, a new prokinetic agent formulated with Pharbitis Semen and Corydalis Tuber. *Phytomedicine* 2008; **15**: 836-843 [PMID: 18490147 DOI: 10.1016/j.phymed.2008.02.019]
- 2 Lee TH, Kim KH, Lee SO, Lee KR, Son M, Jin M. Tetrahydroberberine, an isoquinoline alkaloid isolated from corydalis tuber, enhances gastrointestinal motor function. *J Pharmacol Exp Ther* 2011; **338**: 917-924 [PMID: 21659472 DOI: 10.1124/jpet.111.182048]
- 3 Lee TH, Son M, Kim SY. Effects of corydaline from Corydalis tuber on gastric motor function in an animal model. *Biol Pharm Bull* 2010; **33**: 958-962 [PMID: 20522959]
- 4 Kim ER, Min BH, Lee SO, Lee TH, Son M, Rhee PL. Effects of DA-9701, a novel prokinetic agent, on gastric accommodation in conscious dogs. *J Gastroenterol Hepatol* 2012; **27**: 766-772 [PMID: 21916991 DOI: 10.1111/j.1440-1746.2011.06924.x]
- 5 Ozaki A, Sukamoto T. Improvement of cisplatin-induced emesis and delayed gastric emptying by KB-R6933, a novel 5-HT3 receptor antagonist. *Gen Pharmacol* 1999; **33**: 283-288 [PMID: 10480662]
- 6 Schmidt PT, Abrahamsson H, Dolk A, Hausken T, Karling P, Lindberg G, Nyhlin H, Ohlsson B, Simrén M, Sjölund K, Stotzer PO, Törnblom H. Methods to assess gastric motility and sensation. *Scand J Gastroenterol* 2008; **43**: 1285-1295 [PMID: 18618332 DOI: 10.1080/00365520802240263]
- 7 Symonds EL, Butler RN, Omari TI. Assessment of gastric emptying in the mouse using the [ $^{13}\text{C}$ ]-octanoic acid breath test. *Clin Exp Pharmacol Physiol* 2000; **27**: 671-675 [PMID: 10972530]
- 8 Symonds E, Butler R, Omari T. Noninvasive breath tests can detect alterations in gastric emptying in the mouse. *Eur J Clin Invest* 2002; **32**: 341-344 [PMID: 12027874]
- 9 Schoonjans R, Van Vlem B, Van Heddeghem N, Vandamme W, Vanholder R, Lameire N, Lefebvre R, De Vos M. The  $^{13}\text{C}$ -octanoic acid breath test: validation of a new noninvasive method of measuring gastric emptying in rats. *Neurogastroenterol Motil* 2002; **14**: 287-293 [PMID: 12061914]
- 10 Choi KM, Zhu J, Stoltz GJ, Vernino S, Camilleri M, Szurszewski JH, Gibbons SJ, Farrugia G. Determination of gastric emptying in nonobese diabetic mice. *Am J Physiol Gastrointest Liver Physiol* 2007; **293**: G1039-G1045 [PMID: 17884976 DOI: 10.1152/ajpgi.00317.2007]
- 11 Kashyap PC, Choi KM, Dutta N, Linden DR, Szurszewski JH, Gibbons SJ, Farrugia G. Carbon monoxide reverses dia-

- betic gastroparesis in NOD mice. *Am J Physiol Gastrointest Liver Physiol* 2010; **298**: G1013-G1019 [PMID: 20378827 DOI: 10.1152/ajpgi.00069.2010]
- 12 **Desai KH**, Sato R, Schauble E, Barsh GS, Kobilka BK, Bernstein D. Cardiovascular indexes in the mouse at rest and with exercise: new tools to study models of cardiac disease. *Am J Physiol* 1997; **272**: H1053-H1061 [PMID: 9124413]
- 13 **Ghoos YF**, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, Vantrappen G. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. *Gastroenterology* 1993; **104**: 1640-1647 [PMID: 8500721]
- 14 **Tack J**, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional gastroduodenal disorders. *Gastroenterology* 2006; **130**: 1466-1479 [PMID: 16678560 DOI: 10.1053/j.gastro.2005.11.059]
- 15 **Talley NJ**, Locke GR, Lahr BD, Zinsmeister AR, Tougas G, Ligozio G, Rojavin MA, Tack J. Functional dyspepsia, delayed gastric emptying, and impaired quality of life. *Gut* 2006; **55**: 933-939 [PMID: 16322108 DOI: 10.1136/gut.2005.078634]
- 16 **Galligan JJ**, Vanner S. Basic and clinical pharmacology of new motility promoting agents. *Neurogastroenterol Motil* 2005; **17**: 643-653 [PMID: 16185302 DOI: 10.1111/j.1365-2982.2005.00675.x]
- 17 **Flockhart DA**, Desta Z, Mahal SK. Selection of drugs to treat gastro-oesophageal reflux disease: the role of drug interactions. *Clin Pharmacokinet* 2000; **39**: 295-309 [PMID: 11069215]
- 18 **Drolet B**, Rousseau G, Daleau P, Cardinal R, Turgeon J. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. *Circulation* 2000; **102**: 1883-1885 [PMID: 11034933]
- 19 **Cann PA**, Read NW, Holdsworth CD. Galactorrhoea as side effect of domperidone. *Br Med J (Clin Res Ed)* 1983; **286**: 1395-1396 [PMID: 6404476]
- 20 **Hung TM**, Ngoc TM, Youn UJ, Min BS, Na M, Thuong PT, Bae K. Anti-amnestic activity of pseudocoptisine from *Corydalis Tuber*. *Biol Pharm Bull* 2008; **31**: 159-162 [PMID: 18175962]
- 21 **Sagara K**, Ito Y, Ojima M, Oshima T, Suto K, Misaki T, Ito-kawa H. Quantitative analysis of tertiary and quaternary alkaloids in *Corydalis Tuber* by ion-pair high-performance liquid chromatography and its application to an oriental pharmaceutical preparation. *Chem Pharm Bull (Tokyo)* 1985; **33**: 5369-5374 [PMID: 3833383]
- 22 **Matsuda H**, Shiimoto H, Naruto S, Namba K, Kubo M. Anti-thrombic action of methanol extract and alkaloidal components from *Corydalis tuber*. *Planta Med* 1988; **54**: 27-33 [PMID: 3375333 DOI: 10.1055/s-2006-962324]
- 23 **Saito SY**, Tanaka M, Matsunaga K, Li Y, Ohizumi Y. The combination of rat mast cell and rabbit aortic smooth muscle is the simple bioassay for the screening of anti-allergic ingredient from methanolic extract of *Corydalis tuber*. *Biol Pharm Bull* 2004; **27**: 1270-1274 [PMID: 15305035]
- 24 **Choi MG**, Rhee PL, Park H, Lee OY, Lee KJ, Choi SC, Seol SY, Chun HJ, Rew JS. Randomized, controlled, multi-center trial comparing the safety and efficacy of DA-9701 and itopride hydrochloride in patients with functional dyspepsia: a non-inferiority trial. *J Gastroen Hepatol* 2011; **26** (Suppl. 5): 184
- 25 **Bennink RJ**, De Jonge WJ, Symonds EL, van den Wijngaard RM, Spijkerboer AL, Benninga MA, Boeckstaens GE. Validation of gastric-emptying scintigraphy of solids and liquids in mice using dedicated animal pinhole scintigraphy. *J Nucl Med* 2003; **44**: 1099-1104 [PMID: 12843228]

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