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A Study on the Efficacy of Proton Pump Inhibitors in *Helicobacter pylori*-Negative Primary Care Patients with Dyspepsia in Japan

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Background/Aims: There have been few studies on the efficacy of proton pump inhibitors and the doses required to treat dyspeptic symptoms observed in clinical practice. The aim of this study was to compare the efficacy of different doses of omeprazole and different administration methods in *Helicobacter pylori*-negative, dyspeptic patients. **Methods:** Patients with chronic upper abdominal symptoms within the previous 3 months were randomly divided into three groups: a daily, omeprazole 20 mg treatment group (OPZ20, n=61); a daily, omeprazole 10 mg treatment group (OPZ10, n=72); and an on-demand omeprazole 20 mg treatment group (on-demand, n=62). After 4 weeks of administration of the drug, symptom improvement rates were evaluated based on the Overall Global Severity score. **Results:** The rates of symptom improvement after 4 weeks of treatment were 65.6% (40/61) in the OPZ20 group, 47.2% (34/72) in the OPZ10 group, and 50.0% (31/62) in the on-demand group. The OPZ20 group exhibited a significantly higher improvement rate (p=0.034) than the OPZ10 group. The OPZ20 group had significant improvements in regurgitation, postprandial fullness, vomiting, and bloating compared with the OPZ10 group. **Conclusions:** Daily treatment with 20 mg of omeprazole was efficient in treating upper abdominal symptoms. Trial registration: ClinicalTrials.gov, number UMIN000002621. **(Gut Liver 2013;7:16-22)**

Key Words: Dyspepsia; Proton pump inhibitors; Omeprazole; Primary health care

INTRODUCTION

Functional dyspepsia (FD) is a symptomatically defined clinical disorder, of which the diagnosis is based on chronic or recurrent symptoms thought to originate from the upper gastrointestinal (GI) tract, with the absence of organic diseases likely to explain the symptoms.[1] In addition, according to the Rome III criteria,[2] there is a new classification including two distinct diagnostic categories, i.e., postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), which indicate meal-related and unrelated symptoms, respectively. The primary symptom of FD is epigastric pain or discomfort and other symptoms include excessive burping/belching, upper abdominal bloating, nausea, and a feeling of abnormal or slow indigestion or early satiety.

Dyspepsia is a relatively common health problem in the world. The reported prevalence of this condition in Japan is 13%[3] and a rate of 28%[4] has been shown in an international surveillance study. In addition, it is estimated that 20% to 25% of the population in Western countries is affected by dyspepsia at any time.[5,6] Although mortality related to dyspepsia is rare, the burden on health-care systems is substantial due to the chronic and recurrent nature of this disorder. FD, which is a common condition found in primary care patients, decreases a person's quality of life and results in huge economic loss because of direct expenses from medical care and indirect costs from sick leaves and sickness pensions.

Gastroesophageal reflux disease (GERD), peptic ulcer diseases, and FD are very prevalent in outpatient settings. These acid-related and/or functional disorders of the upper GI tract are currently treated with antisecretory compounds, including histamine H_2-receptor antagonists (H_2RA) and proton pump inhibitor (PPI).[7,8] The efficacy of PPI in FD is well-known. There are many

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well designed studies, including meta-analysis.[9-13] PPIs are more potent in reducing gastric acid than H_2RAs; therefore, they are the most important drugs in practical medicine. In FD patients, among various medications examined in clinical trials, both PPIs and prokinetic therapies have demonstrated to be superior to placebo.[13-16] However, a standard management modality for FD has not yet been established. A recent study[17] showed that treatment with omeprazole provides superior symptom relief compared to ranitidine, cisapride, and placebo treatment in *Helicobacter pylori*-negative dyspeptic patients receiving primary care in Canada. However, the management of *H. pylori*-negative primary care patients with uninvestigated dyspepsia has not been studied in Japan.

The objective of our study was to compare the efficacy of different doses of omeprazole and different administration methods in *H. pylori*-negative dyspeptic patients at 4 weeks of treatment.

MATERIALS AND METHODS

1. Study design

This was a multicenter, single-blind (only patients were blinded) designed study. Allocation to treatment was assigned in equal numbers (1:1:1) using a centrally generated randomization list stratified for each center in blocks of 3. All patients remained blinded to treatment allocation for the duration of the study. Patients were enrolled at three centers (two hospitals and one primary clinic) from April 2009 until September 2009. The study protocol was approved by the local ethics committees, and written informed consent was obtained from each patient.

2. Selection of patients

The age range of the patients was from 20 to 65 years old, and patients had uninvestigated chronic or recurrent upper GI symptoms of stomach pain, heartburn, acid regurgitation, postprandial fullness, vomiting, belching, early satiety, or bloating within the past 3 months. The Global Overall Symptom (GOS) score[18] was recorded at baseline. Moderate to severe symptoms were defined as GOS score of 4 and above in patient-reported symptom questionnaires using a 7-point Likert scale. Patients with "alarm" symptoms (such as vomiting, evidence of bleeding, and inadvertent weight loss) warranting an endoscopy were excluded. Patients were also excluded if they had undergone investigations by upper endoscopy and/or GI barium studies within 3 months prior to randomization. They were also excluded if they had taken any GI drugs, antidepressants, steroids, nonsteroidal anti-inflammatory drugs, aspirin, or bisphosphonates. However, patients could be enrolled if the drugs were washed out for 1 week before entry and discontinued during the study period. The *H. pylori* infection status was evaluated by employing a 20-minute immunochromatography method for the presence of anti-*H. pylori* immunoglobulin G in urine (RAPIRUN® *H. pylori* Antibody; Otsuka Pharmaceutical Co., Tokyo, Japan).[19]

3. Study protocol

After we obtained informed consent from the patients, baseline severity of symptoms was recorded over a 2-week observation period. Then, we performed the *H. pylori* diagnostic test. If the result was positive for *H. pylori*, the patient was excluded from the study. Eligible patients were randomized to a 4-week treatment course with 20 mg omeprazole (OPZ20, as one tablet), 10 mg omeprazole (OPZ10, as one tablet), or on-demand 20 mg omeprazole (on-demand, as one tablet). We defined the method of on-demand therapy in FD according to the method of GERD,[20] as follows; the method of on-demand use was explained to the patients in the following way: the patient takes one tablet when the patient complained of troublesome symptoms; however, the dose did not exceed one tablet per day. If moderate or severe symptoms persisted for 3 consecutive days during the maintenance phase of the study, patients were classified as having symptomatic relapse and were requested to attend the hospital for an extra study visit. Other therapies included no rescue medication. Patient compliance was assessed using pill count of returned medication. Patients were considered to have complied with the treatment if they had taken at least 75% of the dispensed tablets.

We evaluated the symptoms of the patients when they visited the clinic or hospital again after 4 weeks. If medications other than the study drugs were prescribed for dyspepsia, the study drugs were discontinued and the patient was classified as treatment failure. These patients remained in the study and information regarding concomitant medications, tests performed, referrals to specialists, and adverse events was recorded.

4. Outcome measures

The primary outcome measure of the study was the GOS score.[18] This method measured dyspepsia symptoms over the preceding 4 weeks using a 7-point Likert scale. Severity ranged from 1) no problems, 2) minimal problems—can be easily ignored without effort, 3) mild problems—can be ignored with effort, 4) moderate problems—cannot be ignored but do not influence daily activities, 5) moderately severe problems—cannot be ignored and occasionally limit daily activities, 6) severe problems—cannot be ignored and often limit concentration on daily activities to, and 7) very severe problems—cannot be ignored and markedly limit daily activities and often require rest.

We measured the outcome before the study and after 4 weeks of treatment using this score. For the primary outcome measure, sufficient symptom relief was defined as a score of either 1 (none) or 2 (minimal) on the GOS score after 4 weeks of treatment. The proportion of patients becoming completely asymptomatic (GOS=1) was determined as a secondary outcome. In addition, for the secondary outcome measure, symptom aggravation was defined as an increase in the GOS score by 2 and more after

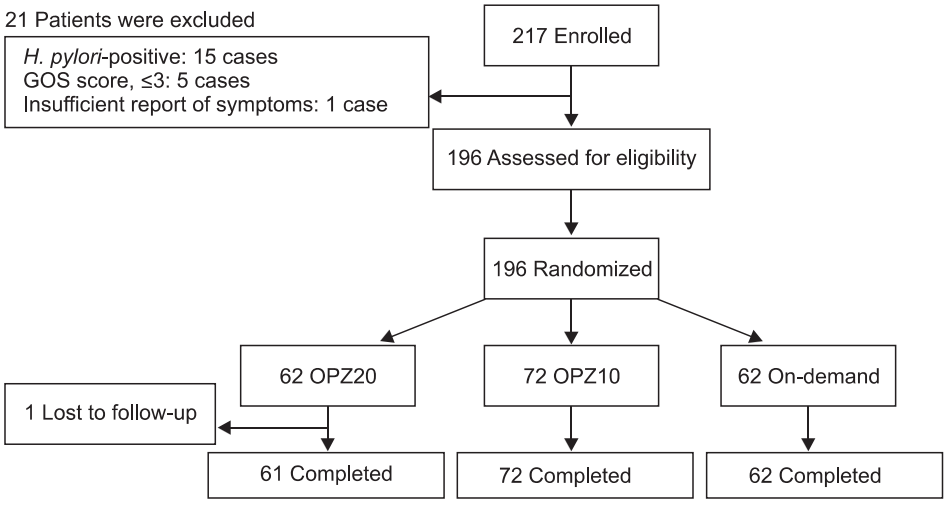

Fig. 1. Flow diagram of study patients.
GOS, Global Overall Symptom; OPZ, omeprazole.

treatment as compared with the score at entry. At the visits, including the baseline visit, patients were asked to rate the severity of a specific dyspeptic symptom (stomach pain, heartburn, acid regurgitation, postprandial fullness, vomiting, belching, early satiety, or bloating) over 1 month, using the same 7-point Likert scale used for evaluation of the GOS. For the secondary outcome measure, improvement of each symptom was also defined as decrease in the GOS score by 2 and more after treatment as compared with the score at entry.

5. Statistical evaluation

The proportion of successfully treated patients was compared for all treatment groups. Comparison between sufficient symptom relief and complete symptom relief of each drug group was performed by using chi-square test and correction of multiplicity was made using the Bonferroni correction. In addition, the proportion of improvement of each symptom after treatment was compared for all treatment groups using the same method. Before we started the study, it was decided that the p-value for the main comparison using the GOS score be corrected for multiplicity using the Bonferroni correction. All p-values for the primary and secondary outcome measures (GOS response at 4 weeks) were considered significant at $p<0.05$.

RESULTS

The flow chart in Fig. 1 describes the patients of the study. Of the 217 patients (82 male, 135 female; age range, 20 to 64 years; mean age, 44.5 years) who were enrolled at baseline observation, 196 were randomized to one of the three treatment groups. Of the 21 patients who were excluded, 15 were *H. pylori*-positive (presence of urinary anti-*H. pylori* antibody), five had low scores on the symptom scale (GOS score, ≤3), and one had an insufficient report of symptoms. One patient in the OPZ20 group was lost during the follow-up; therefore, 61 patients in the OPZ20 group, 72 in the OPZ10 group, and 62 in the on-demand group completed the study. Blinding of the site personnel to the study results for these patients was maintained until the end of the study. All patients' compliance was good on the basis of the returned pill count.

Table 1. Demographic Characteristics of Each Treatment Group

Characteristic	OPZ20	OPZ10	On-demand
Gender			
Male	24 (33.8)	30 (42.3)	18 (23.9)
Female	37 (30.1)	42 (34.1)	44 (35.8)
Age			
<39 yr	32 (33.3)	35 (36.5)	29 (30.2)
40-50 yr	16 (32.0)	17 (34.0)	17 (34.0)
>60 yr	13 (27.1)	20 (41.7)	16 (31.2)
Mean±SD	42.1±17.9	46.1±17.7	43.9±15.7
BMI			
BMI <20	36 (41.4)	25 (28.7)	26 (29.9)
20≤BMI<25	19 (20.7)	39 (44.8)	31 (34.5)
BMI≥25	6 (31.6)	8 (42.1)	5 (26.3)
Mean±SD	20.3±3.5	21.5±2.9	20.9±2.5
Smoking			
None	44 (28.9)	56 (36.8)	52 (34.3)
<20 cigarettes	12 (44.4)	9 (33.3)	6 (22.3)
≥20 cigarettes	5 (33.3)	7 (50.0)	4 (16.7)
Alcohol drinking			
None	43 (34.4)	42 (33.6)	41 (32.0)
Occasionally	10 (21.3)	23 (48.9)	14 (29.8)
Every day	8 (36.4)	7 (31.8)	7 (31.8)

Data are presented as number (%) or mean±SD.
OPZ, omeprazole; SD, standard deviation; BMI, body mass index.

The demographic baseline characteristics of the patients from each group are shown in Table 1. We compared the difference in gender, age, body mass index, smoking habit, and alcohol

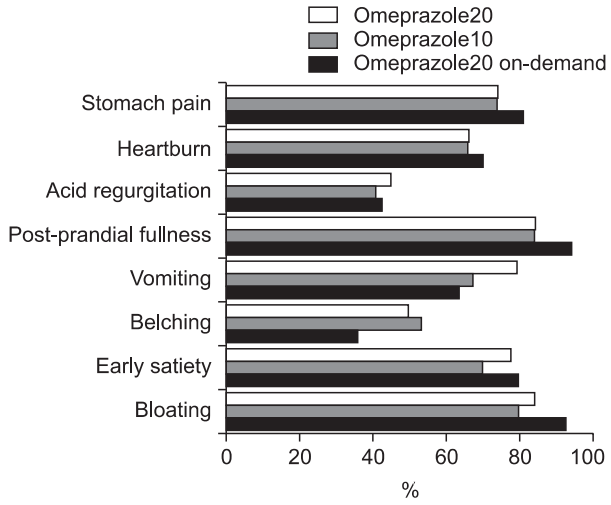

Fig. 2. Frequency of symptoms in each treatment group at baseline. The main bothersome symptoms were postprandial fullness, bloating, and stomach pain.

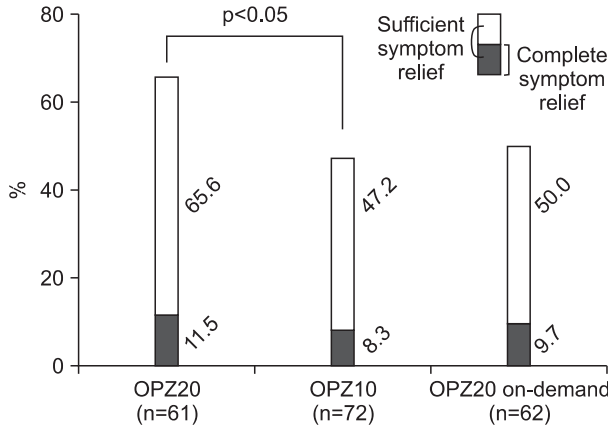

Fig. 3. Percentage of patients exhibiting sufficient symptom relief after 4 weeks of treatment. The omeprazole (OPZ)20 group exhibited significantly better results than the OPZ10 group ($p<0.05$) with respect to the primary outcome measure of symptom relief (Global Overall Symptom ≤2).

Table 2. Rate of Improvement after 4 Weeks of Treatment in Each Group

Symptom	Treatment group	Rate of improvement, %	No.	No. of patients with improvement	p-value (vs OPZ20)
Stomach pain	OPZ20	82	54	44	
	OPZ10	67	63	42	0.07
	On-demand	75	55	41	0.382
Heartburn	OPZ20	83	54	45	
	OPZ10	68	66	45	0.057
	On-demand	73	60	44	0.198
Regurgitation	OPZ20	85	53	45	
	OPZ10	68	63	43	0.037
	On-demand	75	56	42	0.198
Postprandial fullness	OPZ20	84	55	46	
	OPZ10	68	68	46	0.042
	On-demand	75	60	45	0.255
Vomiting	OPZ20	76	59	45	
	OPZ10	56	68	38	0.016
	On-demand	63	59	37	0.110
Belching	OPZ20	79	56	44	
	OPZ10	66	67	44	0.114
	On-demand	70	57	40	0.307
Early satiety	OPZ20	83	54	45	
	OPZ10	72	65	47	0.153
	On-demand	76	58	44	0.328
Bloating	OPZ20	89	54	48	
	OPZ10	61	67	41	0.001
	On-demand	76	58	44	0.072

OPZ, omeprazole.

habit among the three treatment groups. At baseline, there were no statistically significant differences among the treatment groups. The demographic baseline characteristics were well balanced.

Table 3. Percentage of Patients Showing Symptom Aggravation after 4 Weeks of Treatment

	Total no. of patients	No. of patients with aggravation	Rate, %
OPZ20	61	0	0.0
OPZ10	72	0	0.0
On-demand	62	1	1.6

OPZ, omeprazole.

The frequencies of symptoms at baseline of each group are shown in Fig. 2. The main bothersome symptoms were postprandial fullness, bloating, and stomach pain. However, there were no statistically significant differences among the treatment groups at baseline.

After 4 weeks of treatment, OPZ20 was superior compared to the other groups; in particular, it was significantly better than OPZ10 ($p<0.05$) when considering the primary outcome measure of symptom relief (GOS ≤ 2). For responders (GOS ≤ 2) after 4 weeks of treatment, the results for the OPZ20, OPZ10, and on-demand groups were 65.6% (40/61), 47.2% (34/72), and 50.0% (31/62), respectively, according to the per protocol analysis. For complete responders (GOS=1), the results for the OPZ20, OPZ10, and on-demand groups were 11.5% (7/61), 8.3% (6/72), and 9.7% (6/62), respectively. There were no significant differences among the three groups (Fig. 3).

The rate of improvement after 4 weeks of treatment in each group is shown in Table 2. For OPZ20 patients with acid regurgitation (45/53, 85%; p=0.037), postprandial fullness (46/55, 84%; p=0.042), vomiting (45/59, 76%; p=0.016), and bloating (48/54, 84%; p=0.001), OPZ20 treatment was more effective than OPZ10 treatment. There was no difference among the treatment groups with regard to other symptoms. The rate of symptom aggravation after 4 weeks of treatment in each group is shown in Table 3. Only one patient in the on-demand group had symptom aggravation during the study period; however, that patient completed the study without any additional medications. In addition, all patients of the three groups did not receive other medications, did not undergo other tests, were not referred to specialists, and did not experience adverse events throughout the study period.

DISCUSSION

Our results demonstrated that treatment with omeprazole showed efficacy for upper abdominal symptoms relief in *H. pylori*-negative primary care patients with uninvestigated dyspepsia. In particular, omeprazole 20 mg was more effective for treatment of acid regurgitation, postprandial fullness, vomiting, and bloating than omeprazole 10 mg. However, there was no significant difference between omeprazole 20 mg and on-demand therapy.

van Zanten *et al*.[17] (CADET-HN study) showed that treatment with omeprazole provides superior symptomatic relief compared to placebo in the treatment of *H. pylori*-negative primary care patients with uninvestigated dyspepsia. We compared the efficacy of different doses of omeprazole (20 and 10 mg) and different administration methods (daily and on-demand with omeprazole 20 mg) in *H. pylori*-negative dyspeptic patients at 4 weeks of treatment in our study, which is different from the CADET-HN study. We selected *H. pylori*-negative dyspeptic patients whose number may increase in the future in Japan. Recently, several studies showed that the rate of *H. pylori* infection gradually decreases in Japan.[21-23] Our recent study[24] showed that over a period of 25 years, between 1981 and 2005, the percentage of patients complaining of heartburn increased almost five-fold, and with respect to endoscopic findings, the prevalence of peptic ulcers decreased, whereas the number of patients with no abnormalities and erosive esophagitis increased. However, the rate of *H. pylori* infection and prevalence of gastric cancer are still high in the old generation in Japan;[25] therefore, we selected dyspeptic patients whose age range was from 20 to 65 years. Considering these epidemiological results, it is possible to consider that, in the future in Japan, there will be fewer patients with peptic ulcers and more GERD patients or dyspeptic patients who display no endoscopic abnormalities.[22-24]

The optimum therapeutic strategy for dyspepsia has not been well established in Japan. Recently, several pathophysiological mechanisms have been suggested, i.e., delayed gastric emptying, impaired gastric accommodation to a meal, hypersensitivity to gastric distension, *H. pylori* infection, altered duodenal sensitivity to lipids or acid, abnormal duodeno-jejunal motility or central nervous system dysfunction may play a role in dyspeptic symptoms.[26] Therefore, it has been suggested that acid-suppressive drugs, novel prokinetics, eradication of *H. pylori*, antidepressants, fundus-relaxing drugs, antagonists of 5-hydroxytryptamine, cholecystokinin receptor antagonists, or traditional Japanese medicine (Kampo) would be efficacious treatment options for dyspeptic patients.[27,28]

One of these mechanisms, the abnormality of gastric acid secretion, plays an important role in the occurrence of dyspepsia. In patients with FD, especially those with EPS, suppression of gastric acid secretion by antisecretory agents such as PPIs or H_2RAs seems to ameliorate epigastric pain or burning, so-called GERD. Furthermore, even in PDS, as the initial gastric acid emptying may play a pathogenetic role on symptom generation through the early onset of duodenal brake, acid suppression might be effective, at least in part, against the bothersome symptom of postprandial fullness.[29] PPIs are among the strongest drugs available for gastric acid suppression. Therefore, as shown in our study, daily treatment with omeprazole 20 mg was more effective, in particular, for acid regurgitation, postprandial fullness, vomiting, and bloating, than that with omeprazole 10 mg.

Unfortunately, our study has several limitations. First, in our methodology, our study was not a double-blind placebo controlled study. We did not select a placebo group or control group in our study. In the future, we will need to evaluate the efficacy of omeprazole for dyspeptic symptoms in a double-blind placebo controlled study. Usually, treatment with placebo showed an efficacy of about 20% to 30% in dyspeptic patients. The CADET-HN study[17] showed that among responders, 51.1% responded to omeprazole treatment and 23.3% responded to placebo treatment. Therefore, in order to evaluate the exact efficacy of omeprazole in patients we will need to include a placebo group in future studies. Secondly, our selected dyspeptic patients did not exactly meet the criteria of the Rome III classification. The subjects of our study were defined as patients with chronic or recurrent upper abdominal symptoms within the past 3 months, although the Rome III classification is based on events that occurred in the past 6 months. However, this aspect needs to be further evaluated for Japanese dyspeptic patients. Recently, Manabe and Haruma[30] proposed that the 6-month period after onset of dyspeptic symptoms, currently required for diagnosis of FD in the Rome III classification, should be shortened in the Japanese population, because for Japanese patients, the period between symptom onset and evaluation in the hospital is usually less than 6 months. Finally, among our selected dyspeptic patients were GERD patients. These patients had upper GI symptoms that included not only stomach pain, postprandial fullness, vomiting, belching, early satiety, or bloating but also heartburn or regurgitation. FD is defined as symptoms that are thought to originate from the gastroduodenal region (in particular, epigastric pain or burning, postprandial fullness or early satiation) with differentiation between PDS and EPS. In our study, we included GERD patients because FD and GERD are among the most widely prevalent upper GI disorders in Japan,[30] as well as in Western countries. In other words, both heartburn and regurgitation are typical symptoms of patients with GERD, and some GERD patients may present with typical FD symptoms such as epigastric pain and epigastric burning without any endoscopic mucosal lesions. On the other hand, some FD patients may have reflux symptoms. Therefore, there is an overlap between dyspeptic and reflux symptoms.

A systematic review[31] demonstrated that on-demand therapy with currently available PPIs appears to be effective in the long-term management of patients with nonerosive reflux disease or mild and uninvestigated forms of GERD. Randomized-controlled clinical trials[32,33] in either form of GERD have shown that PPIs are superior to placebo and H_2RAs for controlling symptoms. However, the efficacy of on-demand therapy with omeprazole for FD is not well known. In the data about GOS and each symptoms, there was no difference of efficacy between continous omeprazole 20 mg therapy and on-demand therapy. In addition, only one patient in the on-demand group had symptom aggravation during the study period. However, major side effects were not observed in the three treatment groups.

In summary, our results demonstrated that treatment with omeprazole was efficient for upper abdominal symptoms relief in *H. pylori*-negative primary care patients with uninvestigated dyspepsia. Dyspeptic patients who experience acid regurgitation, postprandial fullness, vomiting, and bloating may be more applicable to continuous omeprazole 20 mg than omeprazole 10 mg. In the future, we will need to evaluate the long-term efficacy of omeprazole for dyspeptic symptoms.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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