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Original

Comparative Study of a Proton Pump Inhibitor with a Histamine H_2 Receptor Antagonist in Japanese Patients with Functional Dyspepsia

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Abstract: The present study sought to compare the effectiveness of a proton pump inhibitor (PPI) with that of a histamine H_2 receptor antagonist (H2RA) for treating functional dyspepsia (FD) in a real-world setting. A multicenter, open-label, randomized trial was conducted. FD patients were randomly assigned to receive either 20 mg, q.d., omeprazole (OPZ; a PPI) or 150 mg, b.i.d., ranitidine hydrochloride (RAN; an H2RA) for 4 weeks. Any change in the total Gastrointestinal Symptom Rating Scale (GSRS) score (delta) at week 4 was the primary outcome measure. Secondary outcome measures were reductions in scores for individual items on the GSRS at week 4. As a subanalysis, patients were stratified according to *Helicobacter pylori* serology and the analyses were repeated. The mean (±SD) deltas in total GSRS score for the OPZ and RAN groups were 0.8 ± 0.7 and 0.6 ± 0.6, respectively ($P = 0.098$); however, the delta in reflux score between the OPZ and RAN groups differed significantly (1.1 ± 0.7 vs. 0.5 ± 0.5, respectively; $P = 0.001$). There were no significant differences between the two groups in any other scores for individual items on the GSRS. The results of the subanalysis were like those of the main analysis. The PPI and H2RA produced a comparable improvement in symptoms of FD in our patient cohort, thus we propose no advantage would be gained in using a PPI rather than an H2RA.

Key words: functional dyspepsia, gastric acid, histamine H_2 receptor antagonist, proton pump inhibitor, randomized trial

Introduction

Upper abdominal, or dyspeptic, symptoms are a common health problem. Of people attending hospital for an annual medical check-up, rather than a medical consultation, 17% complained of experiencing a dyspeptic symptom once a week[1]. Because dyspeptic symptoms are bothersome and impair quality of life[2], they affect patients' medical seeking behavior. In addition, Okumura

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et al[3] reported that 6.6% of patients presenting for the first time at a hospital department of general medicine complained of dyspeptic symptoms[3].

Dyspeptic symptoms can be a sign of structural diseases, such as peptic ulcer or cancer, although recent cross-sectional studies reported that less than 10% of dyspeptic patients showed macroscopic disease[4,5]. Thus, in most patients, dyspeptic symptoms are "functional", and this subgroup of patients is referred to as having functional dyspepsia (FD)[6].

The pathophysiology underlying FD symptoms remains elusive, with many factors including gastric motor function, gastric acid, visceral perception, and psychosocial factors implicated in generating typical FD[7,8]. Of these, gastric acid is a well-known irritant that could promote upper abdominal symptoms. Although gastric acid constitutively resides in the stomach, Oshima *et al*[9] demonstrated that intragastric perfusion of 0.1 M hydrochloric acid induced a variety of symptoms, including epigastric pain, nausea, bloating, and satiety, particularly in FD subjects. Moreover, Ishii *et al*[10] demonstrated that the duodenum of FD patients was more susceptible to acid than that of healthy volunteers. These data thus suggest gastric acid as a potent therapeutic target in patients with FD symptoms.

Acid-suppressive agents, namely histamine H_2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), have been used historically to treat patients with FD symptoms[11–13]. Both types of medication have clinical benefit in improving symptoms, although it is reasonable to assume that PPIs could be more effective than H2RAs considering that the former shows more potent acid-suppressive effects. This assumption has been supported by randomized controlled trials that showed higher efficacy of PPIs over H2RAs for the management of FD[14–16]. However, these studies were conducted in Western countries, and direct comparative studies between PPIs and H2RAs in Japanese patients are scarce. Thus, the the present study aimed to compare the effectiveness of a PPI with that of an H2RA in Japanese patient presenting with symptoms of FD.

Materials and methods

Study population

From 2006 to 2008, patients between 20 and 80 years of age who were suffering from upper abdominal symptoms were asked to participate in the study. At the initial visit, subjects were interviewed to assess which specific symptom was the predominant, as determined by the attending physician. Because the present study sought to reflect real-world practice, there were no limits imposed on the duration and severity of symptoms when recruiting subjects; however, patients were excluded from the study if they met any of the following criteria: predominant symptom of heartburn; symptoms suggestive of irritable bowel syndrome; comorbid organ failure (e.g., heart, liver, and kidney); on medications that affect gastric acid and upper gastrointestinal symptoms, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and antidepressants; suspected malignant disease; history of gastric surgery; pregnant or lactating; and, alcohol abuse.

Study design

The present study was a multicenter, open-label, randomized trial.

Setting

One tertiary care center and six primary care offices participated in the present study.

Study protocol

Patients underwent esophagogastroduodenoscopy and blood tests to exclude any organic and/or metabolic diseases. *Helicobacter pylori* (HP) infection was determined by serology. The Gastrointestinal Symptom Rating Scale (GSRS) was used to score upper abdominal symptoms, because this questionnaire has been widely used in many clinical trials and has already been validated[17]. The GSRS consists of 15 questions regarding both upper and lower abdominal symptoms, with the responses combined into five scores: reflux, abdominal pain, indigestion, diarrhea, and constipation. Responses to the GSRS are graded using a seven-point Likert-type scale from 1 (no symptoms) to 7 (very troublesome symptoms). After completing the GSRS, patients were randomly assigned to receive either 20 mg, q.d., omeprazole (OPZ), a PPI, or 150 mg, b.i.d., ranitidine hydrochloride (RAN), an H2RA.

These doses of OPZ and RAN are recognized as standard and are demonstrated to be sufficient for treating acid-related disease in Japan[18]. Subjects were allocated to the different groups using a computer-generated randomization list stratified by each institution. Subjects were asked to return on weeks 2 and 4 to complete the GSRS again at both time points. During the study period, patients were not permitted to take medicines that could potentially affect gastric acid and upper abdominal symptoms, such as antacids, prokinetics, NSAIDs, and antidepressants.

Outcome measures and statistical analyses

The primary outcome measure for both groups was the reduction (delta) in total GSRS score (from all 15 questions) at week 4. Secondary outcome measures were reductions in scores for individual items on the GSRS at week 4. Because HP infection affects the action of gastric acid suppressants and provokes upper abdominal symptoms[19,20], patients were also stratified according to HP serology, and the primary and secondary outcome measures were further examined. Nine patients were lost to follow-up at week 4 and missing data were accounted for using the last observation (i.e., at week 2) and a carried forward method. Patient demographics were analyzed using descriptive statistics. For comparisons of numerical and categorical data, the Mann–Whitney *U*-test and Fischer's exact probability test were used respectively, as appropriate. To examine the significance of differences between groups in primary and secondary outcome measures, *t*-tests were used. All tests were two sided and $P < 0.05$ was considered significant. Analysis was based on the full data set. Statistical analyses were performed using JMP Pro 10.0.2 (SAS Institute Inc., Cary, NC, USA). Unless indicated otherwise, data are presented as the mean ± SD.

Ethical considerations

The study protocol was approved by the local ethics committees of the participating institutions (Ethics Committee of Showa University School of Medicine, No 447). All participants provided written informed consent.

Results

Demographics (*Table 1*)

During the study period, 79 patients were recruited to the present study: 40 were from the primary care medical offices and 39 were from the tertiary care center. Mean patient age was 52 ± 15 years, and there were more female than male patients [59 (75%) vs. 20 (25%), respectively]. Approximately one-fifth of patients in both the OPZ and RAN groups were HP seropositive. In terms of the duration of dyspeptic symptoms, symptoms had been present for > 6 months in 37 patients (50%), 3–6 months in 5 patients (4%), 1–3 months in 12 patients (10%), and for < 1 month in 5 patients (5%). There were no significant differences in age, sex, duration of symptoms, and HP seropositivity between the OPZ and RAN groups. At baseline, there was no significant difference in the total GSRS score between the OPZ and RAN groups (2.4 ± 0.7 and 2.5 ± 0.9, respectively; $P = 0.534$).

Primary outcome measure (*Table 2*)

We assigned 41 and 38 patients to the OPZ and RAN groups, respectively. At week 4, although delta for the total GSRS score was greater in the OPZ than the RAN group (0.8 ± 0.7 vs. 0.6 ± 0.6, respectively), the difference did not reach statistical significance ($P = 0.098$).

Secondary outcome measures

Secondary outcome measures were changes in scores (delta) for individual items on the GSRS

Table 1. Demographics and baseline Gastrointestinal Symptom Rating Scale (GSRS) scores in patients allocated to the omeprazole or ranitidine hydrochloride treatment groups (n = 79)

	Omeprazole (n = 41)	Ranitidine (n = 38)	*P* value
Age (years)	54 ± 13	50 ± 16	0.153
No. females	29 (70)	30 (79)	0.447
HP negative	28 (82)	25 (78)	0.762
Duration of symptoms (months)			
< 1	5 (17)	7 (23)	
1–6	5 (17)	6 (19)	0.824
≥ 6	19 (66)	18 (58)	
GSRS at baseline			
Total	2.4 ± 0.7	2.5 ± 0.9	0.534
Reflux	2.6 ± 1.2	2.5 ± 1.3	0.671
Abdominal pain	2.6 ± 0.9	3.0 ± 1.2	0.074
Indigestion	2.6 ± 1.1	2.7 ± 1.2	0.757
Diarrhea	1.8 ± 1.0	2.2 ± 1.2	0.118
Constipation	2.2 ± 1.1	2.2 ± 1.2	0.965

Data are presented as the mean ± SD or as n (%).
HP, *Helicobacter pylori*.

relating to upper abdominal symptoms, including reflux, abdominal pain, and indigestion (Table 2). At week 4, the GSRS reflux score delta was significantly greater in the OPZ than the RAN group (1.14 ± 0.7 vs. 0.5 ± 0.5, respectively; $P = 0.001$); however, there were no significant differences between the OPZ and RAN groups in the deltas for abdominal pain score (1.0 ± 0.8 vs. 0.9 ± 0.1, respectively; $P = 0.6$) or indigestion score (1.0 ± 0.9 and 0.6 ± 0.9, respectively; $P = 0.14$).

Subanalyses (Tables 3, 4)

The number of HP-seropositive patients was too small for statistically significant subanalyses, only data from the seronegative patients were used in the final subanalyses (Table 3), with 28 and 25 patients assigned to the OPZ group and RAN group, respectively. As indicated in Table 4, the

Table 2. Reduction in Gastrointestinal Symptom Rating Scale (GSRS) scores (total and for individual items on the GSRS) at week 4 in patients allocated to the omeprazole or ranitidine hydrochloride treatment groups

	Omeprazole (n = 41)	Ranitidine (n = 38)	*P* value
Total score	0.8 ± 0.7	0.6 ± 0.6	0.098
Acid regurgitation	1.1 ± 0.7	0.5 ± 0.5	0.001
Abdominal pain	1.0 ± 0.8	0.9 ± 0.1	0.600
Indigestion	1.0 ± 0.9	0.6 ± 0.9	0.140
Diarrhea	0.5 ± 0.9	0.3 ± 1.0	0.538
Constipation	0.4 ± 1.1	0.3 ± 0.8	0.668

Data are the mean ± SD. [A]Primary outcome measure.

Table 3. Demographics and baseline Gastrointestinal Symptom Rating Scale (GSRS) scores in *Helicobacter pylori*-seronegative patients (n = 53)

	Omeprazole (n = 28)	Ranitidine (n = 25)	*P* value
Age (years)	55 ± 13	48 ± 17	0.076
No. females	20 (71)	18 (72)	0.963
Duration of symptoms (months)			
< 1	3 (14)	6 (27)	
1–6	6 (28)	7 (31)	0.374
≥ 6	12 (58)	9 (42)	
Baseline GSRS score			
Total	2.4 ± 0.8	2.5 ± 0.9	0.520
Reflux	2.5 ± 1.2	2.4 ± 1.4	0.830
Abdominal pain	2.5 ± 1.0	3.0 ± 1.3	0.066
Indigestion	2.7 ± 1.1	2.7 ± 1.3	0.847
Diarrhea	1.9 ± 1.0	2.3 ± 1.3	0.159
Constipation	2.2 ± 1.1	2.2 ± 1.2	0.999

Data are presented as the mean ± SD or as n (%).

Table 4. Reduction in Gastrointestinal Symptom Rating Scale (GSRS) scores (total and for individual items on the GSRS) at week 4 in *Helicobacter pylori*-seronegative patients

	Omeprazole (n = 28)	Ranitidine (n = 25)	*P* value
Total score	0.8 ± 0.7	0.5 ± 0.6	0.131
Acid regurgitation	1.0 ± 1.0	0.4 ± 0.8	0.009
Abdominal pain	1.0 ± 0.8	1.0 ± 0.9	0.876
Indigestion	1.0 ± 0.8	0.6 ± 1.0	0.110
Diarrhea	0.5 ± 0.9	0.4 ± 1.0	0.494
Constipation	0.5 ± 1.2	0.3 ± 0.8	0.601

Data are the mean ± SD.

results of subanalyses were consistent with those of the main analyses, with no significant difference in the delta for the total GSRS score between the OPZ and RAN groups (0.8 ± 0.7 vs. 0.5 ± 0.6, respectively; $P = 0.131$) or in the abdominal pain and indigestion scores individually ($P = 0.876$ and $P = 0.110$, respectively), whereas there was a statistically significant difference between the two groups in the reflux score.

Discussion

With no evidence of structural disease, the specific symptoms of FD were the major targets of treatment in the present study. Symptom improvement, as measured by the total GSRS score, was comparable between the two groups; however, comparing individual symptom scores on the GSRS revealed a significantly greater reduction in reflux score for the OPZ group compared to the RNA patients, with no significant differences between the two groups for any of the other individual symptom scores. Based on these results, we found no clear benefit in using a PPI for the treatment of FD symptoms in place of an H2RA.

This study was not designed to investigate the effect of gastric acid inhibition on FD symptoms because a placebo arm was not included. Nevertheless, there were significant decreases in the total GSRS score, as well as in the individual reflux, abdominal pain, and indigestion scores, in both groups at week 4 compared with week 0 (data not shown), indicating that gastric acid inhibition certainly helps improve dyspeptic symptoms. Considering that PPIs more potently inhibit gastric acid secretion than H2RAs, the superiority of PPIs in improving dyspeptic symptoms was anticipated; however, we found no such differences in the present study groups. One possible explanation is that, as mentioned earlier, the mechanisms responsible for the generation of FD symptoms are multifactorial, and FD might not be a primarily gastric acid-related condition. Based on that proposal, gastric acid inhibition by the H2RA might have been sufficient to improve the symptoms. Indeed, Japanese clinical practice guidelines for FD do not mention which agent should be used as first-line therapy[21].

The results of the present study are not in agreement with previous randomized controlled trials in Western populations that showed superior effectiveness of PPIs over H2RAs in the

management of FD[14–16]. There are several reasons for the apparent discrepancy. First, in the present study we did not place any limits on symptom severity when considering patients for inclusion, whereas previous studies recruited sicker patients with moderate to severe symptoms at the time of treatment[14–16]. The milder the initial symptoms are, the more difficult it is to recognize therapeutic gain. Second, there are differences between previous studies in the methods used to assess symptoms following intervention. In the present study we used the GSRS and compared reductions (delta) in scores between the groups, whereas previous studies used different questionnaires, such as the Global Overall Severity (GOS) score[16], or physicians' assessments of symptoms[14]. Furthermore, in contrast to the present study, the outcome measure in previous studies was the proportion of patients who achieved complete and/or substantial symptomatic resolution[14–16]. Third, there are differences in inclusion criteria between studies, and therefore the study populations. For example, Jones and Baxter[14] recruited either reflux-like or ulcer-like dyspeptic patients, but not those with dysmotility-like disease, whereas the patients in the study of Mason *et al*[15] had benefited from antacid prior to being recruited to the study. Thus, both these former study populations would have been susceptible to acid-suppressive agents, which may differ from the present study population. Finally, dyspepsia in Western patients could be more acid related than in Japanese patients. For example, Mahadeva *et al*[22] reported that the prevalence of gastroesophageal reflux disease (GERD) among dyspeptic patients is more common in British than South-East Asian subjects. Taking these factors into consideration, it is not reasonable to compare the present study with previous reports.

Comparing scores for individual items on the GSRS, we found that the PPI significantly reduced the reflux score relative to the H2RA, although the two agents were comparable for the other individual score items tested. Although patients who had predominantly reflux-associated symptoms at the time of recruitment were excluded from the present study, it has been shown recently that a substantial number of patients with FD also have GERD[23]. Given that the therapeutic benefit of PPIs for GERD is definitely greater than that of H2RAs[24], the findings of the present study are quite reasonable. Indeed, Carlsson *et al*[25] demonstrated significant symptom relief with the use of PPIs in FD patients who were prespecified to have reflux-predominant symptoms. Considering the high prevalence of overlapping FD and GERD, the choice of a PPI as first-line therapy could be justified in a subgroup of dyspeptic patients with concomitant GERD symptoms.

The reductions in symptom scores for abdominal pain and indigestion, two major symptoms in FD, were comparable between the OPZ and RAN groups in the present study. Historically, gastric acid and delayed gastric emptying have been therapeutic targets for abdominal pain and indigestion, respectively, prompting the use of gastric acid suppressants and prokinetics[26]. Consistent with these observations, Matsueda *et al*[27] reported that the novel prokinetic, acotiamide, was effective in FD patients who fulfilled the Rome Ⅲ diagnostic criteria for postprandial distress syndrome; however, recent studies demonstrated that specific dyspeptic symptoms do not reflect the underlying pathological mechanism[28, 29]. In addition, we did not prespecify the presence of dyspeptic symptoms in the inclusion criteria because of our aim to compare the

effectiveness of the PPI and H2RA in a real-world setting. Such patient heterogeneity could have resulted in the lack of difference between the PPI and H2RA in the present study.

Because HP infection has a considerable effect on upper gastrointestinal physiology, it is conceivable that HP status affects the pharmacological properties of PPIs and H2RAs. Although Blum *et al* reported that a therapeutic benefit of PPIs for FD was observed in HP-positive patients[30], the CADHET study, which recruited HP-negative patients, also demonstrated the superiority of PPIs over H2RA in FD[16]. In the present study, the results in HP-negative patients were similar to those in the total patient group, indicating that HP infection is less likely to affect the short-term effect of gastric acid suppressants on dyspeptic symptoms. The frequency of HP-positive patients in the present study was 13%, similar to that previously reported in the Japanese population[31], so that our findings may be generalizable to the Japanese population. However, because of the small sample size of the present study, larger studies are needed to confirm our findings.

The present study has several limitations. First and most importantly, the present study lacks statistical power. At the time of study design, we could not find any large-scale studies assessing the effectiveness of PPIs or H2RAs on FD in the Japanese population, so that estimating the number of patients needed to provide power in present study was difficult. Second, other potent confounders, including comorbidities, particularly psychiatric diseases, family history, and drug compliance, were not included in the analyses. Third, this was an open-label study, and thus could have affected patients' perceptions. Nonetheless, the present study is the first reported to directly he effectiveness of a PPI and an H2RA in Japanese FD patient, and the study population appears to be representative of patients in daily clinical practice.

In conclusion, PPI and H2RA produced comparable improvements in FD symptoms in our study cohort. There was seemingly no advantage in using the PPI over the H2RA ; however, a subgroup of dyspeptic patients who also have GERD might benefit more from a PPI.

Conflict of interest disclosure

The authors report no conflict of interest in connection with the publication of this manuscript.

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