Symptom Diversity of Patients with Reflux Esophagitis: Effect of Omeprazole Treatment

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Summary Objective: A number of clinical trials have reported that proton-pump inhibitors are efficacious in the treatment of upper abdominal symptoms, but most of these trials have been carried out in Caucasians. This study investigated the type of upper abdominal symptoms reported by Japanese patients with reflux esophagitis and the efficacy of omeprazole for treating their symptoms.

Methods: A total of 234 patients aged ≥ 20 years with grade A to D reflux esophagitis were enrolled in this multicenter, open study. Patients received omeprazole 10 or 20 mg/day for 4 weeks. Symptom and quality of life questionnaires were administered at baseline, week 2 and week 4.

Results: Among the 221 evaluable patients, almost 70% reported reflux-type symptoms (e.g. regurgitation and heartburn). Ulcer- and dysmotility-type symptoms (e.g. stomach pain and belching) were also common, occurring in 38–62% of patients. After 4 weeks of omeprazole

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Abbreviations: ARD, acid-related disease; FD, functional dyspepsia; GSRS, Gastrointestinal Symptoms Rating Scale; PPIs, proton pump inhibitors; PU, peptic ulcer; QOL, quality of life; RE, reflux esophagitis; SD, standard deviation.

treatment, all symptoms (except anorexia) were improved in approximately 90% of patients. Quality of life was also improved following omeprazole treatment.

Conclusion: Reflux-type symptoms as well as ulcer- and dysmotility-type symptoms were seen frequently in Japanese patients with reflux esophagitis. However, omeprazole improved all symptom types and quality of life in this patient population.

Key Words: Upper abdominal symptoms, reflux esophagitis, functional dyspepsia, omeprazole

Introduction

In Japan, a large number of patients experience upper abdominal symptoms such as heartburn, stomach discomfort and a sensation of fullness. In the majority of patients, symptoms are mild and can be controlled by over-the-counter drugs. The rest of the patients visiting hospitals have severer symptoms and decreased quality of life (QOL) [1, 2], but their symptoms are not always treated satisfactorily. Patients usually have variety of symptoms and it sometimes makes physicians felt difficulty to select adequate treatment unless the symptoms are clearly accounted to organic disease, leaving patients in an undesirable condition.

The pathogenesis of upper abdominal symptoms where no evidence of organic disease is present remains unknown. In the meantime, the concept of functional dyspepsia (FD) has been established whereby patients with a number of upper abdominal symptoms are classified into three subtypes according to the dominant symptoms for treatment purpose, but treatment outcomes are uncertain using this approach [3, 4] because the majority of symptoms overlap across the subtypes of FD [5, 6]. Upper abdominal symptoms are also seen in patients with acid-related disease (ARD) such as peptic ulcer (PU) and reflux esophagitis (RE). Symptoms in such patients are improved according to the treatment of PU or RE by antisecretory agents, suggesting that upper abdominal symptoms are somewhat associated with gastric acid.

Proton pump inhibitors (PPIs) are widely used for treatment of ARD. PPIs show efficacy on the upper abdominal symptoms observed in those patients. PPIs also showed a certain efficacy on symptom control in patients with FD. Positive results of treatment with a PPI for *Helicobacter pylori* (*H. pylori*)-negative dyspepsia has recently been reported in Caucasians; Veldhuyzen van Zanten *et al.* reported that omeprazole was superior to ranitidine, cisapride and placebo [7]. However, it is uncertain whether the Japanese have a similar response because study of PPIs for treatment of upper abdominal symptoms in Japanese population is limited.

We considered it was useful to know the type of upper abdominal symptoms and the treatment effect of PPIs in Japanese patients in order to investigate whether PPIs are effective for the symptoms. The purpose of this study,

therefore, was to confirm symptom variety in patients with RE and to investigate whether symptoms were controlled during 4-weeks treatment with omeprazole.

Materials and Methods

This was a multi-center, open study conducted at 79 centers in Japan from November 2005 to February 2006.

Subjects

Patients were eligible for the study if they were aged 20 years or older and had grade A to D reflux esophagitis (according to the Los Angeles Classification [8]) with one or more upper abdominal symptoms other than heartburn. Patients were excluded if they had been treated with a PPI and/or H₂ receptor antagonists within 1 week prior to enrollment; had a prior history of gastrointestinal tract resections and/or vagotomy; had Zollinger-Ellison syndrome and/or pernicious anemia; and/or had complications of severe liver/kidney/heart disorders. Verbal informed consent was obtained from patients and the ethics committee for each site approved the protocol.

Study design

The schedule of the study is shown in Table 1. At study entry, patient eligibility was determined and an endoscopy was performed. The presence of gastrointestinal symptoms was assessed by a questionnaire, in which pathognomonic symptoms for both reflux-type and ulcer- and dysmotility-type (Table 2) were listed. QOL was measured by patients with the Gastrointestinal Symptoms Rating Scale (GSRS), which is a validated QOL questionnaire designed for gastrointestinal symptoms [9, 10].

Table 1. Summary of items to be evaluated

Parameter	Week 0 (study entry)	2 weeks	4 weeks
Patient background, history	✓		
Endoscopy	✓		
Gastrointestinal symptoms	✓	✓	✓
QoL (GSRS)	✓	✓	✓
Drug dosage/compliance		✓	✓

GSRS = Gastrointestinal Symptoms Rating Scale.

Table 2. Symptom types

Symptom type	Symptoms as listed in the questionnaire
Reflux-type symptoms	Tickling or tingling in the throat
	Feeling that sour contents are coming up from the stomach (regurgitation)
	Feeling that something is stuck in the throat
	Burning sensation in the chest (heartburn)
Ulcer- and dysmotility-type symptoms	Pain in the stomach
	Nausea or feeling sick
	Heavy feeling in the stomach
	Feeling of fullness in the stomach
	Belching
	No appetite (anorexia)

Patients received either omeprazole (AstraZeneca K.K., Osaka, Japan) 10 mg once daily or 20 mg once daily for four weeks. The dosage was decided at the physician's discretion based on the patient's condition. Change of dosage during the study was allowed and date of change of dosage was recorded. Concomitant use of other PPIs or H₂ receptor antagonists during the study period was prohibited.

Efficacy assessment

Treatment response was assessed for the symptoms presented at study entry by a 4-point grade categorical scale (1 = complete relief; 2 = better than before; 3 = no change; 4 = worse than before). In cases of withdrawal, evaluations were made at the point of withdrawal.

The primary efficacy variable was symptom improvement rate at week 4 (i.e. "complete relief" or "better than before"). Symptom improvement rate at week 2, complete symptom relief rate and GSRS score at weeks 2 and 4 were assessed subsequently. Symptom improvement rate and complete symptom relief rate in each dosage were also assessed.

Statistical analysis

Symptom improvement rate, complete symptom relief rate and GSRS scores were assessed descriptively. Symptom improvement rate was shown in two separate figures in accordance with the symptoms as summarized in Table 2; Reflux-type symptoms and ulcer- and dysmotility-type symptoms. For statistical analysis of GSRS scores, Student's t-tests were used. $P < 0.05$ was considered to be statistically significant.

Results

Study population

A total of 234 patients were entered in the study, of which 13 were excluded due to violation of inclusion or exclusion criteria. Of the remaining 221 patients, 58 received omeprazole 10 mg/day and 158 received 20 mg/

Table 3. Baseline characteristics

		Patients (n)	%
Gender	Male	104	47.1
	Female	117	52.9
Age (years)	26–39	25	11.3
	40–59	77	34.8
	60–89	119	53.8
	<65	127	57.5
	≥65	94	42.5
	Mean (SD)	59.1 (13.6)	Not applicable
Body mass index	<20	24	10.9
	21–24	115	52
	≥25	65	29.4
	Mean (SD)	23.8 (3.6)	Not applicable
	Unknown	17	7.7
Smoking (cigarettes/day)	Non-smoker	172	77.8
	<20	20	9
	≥20	24	10.9
	Unknown	5	2.3
Alcohol	None	121	54.8
	Sometimes	44	19.9
	Everyday	53	24
	Unknown	3	1.4
RE grade	A	129	58.4
	B	65	29.4
	C	25	11.3
	D	2	0.9
History of RE (months)	<1	87	39.4
	1 to <6	33	14.9
	≥6	45	20.4
	Unknown	56	25.3
Other gastrointestinal diseases	None	107	48.4
	Gastric ulcer	7	3.2
	Duodenal ulcer	9	4.1
	Atrophic gastritis	49	22.2
	Other	53	24
Initial omeprazole dosage (mg/day)	10	58	26.2
	20	158	71.5
	Other	5	2.3

SD = standard deviation.

day. Baseline characteristics for the 221 patients are presented in Table 3. Patients with a severe grade of RE were limited – only 12% had grade C or D RE. Atrophic gastritis was the most common gastrointestinal complication (22% of patients), whereas peptic ulcer occurred in less than 10% (Table 3).

Fig. 1. Gastrointestinal symptoms reported by patients at baseline.

Fig. 2. Prevalence of gastrointestinal symptoms according to gender (a) and age (b).

Symptoms presented at study entry are shown in Figure 1. The average number of symptoms was 5.4 per patient. The percentage of patients who reported 3 or more symptoms was 92% and who reported 6 or more was 39%.

The most frequent symptoms were reflux-type, “Feeling that sour contents are coming up from the stomach (regurgitation)” and “Burning sensation in the chest (heartburn)”, reported by approximately 70% of patients. While these symptoms were expected in patients with RE, a substantial percentage of ulcer- and dysmotility-type symptoms were also reported (Figure 1).

Symptom prevalence stratified by gender showed that “Heavy feeling in the stomach”, “Feeling that something is stuck in the throat” and “Belching” complaints occurred often in females. Patients aged less than 65 years were more likely to experience “Pain in the stomach”, “Nausea or feeling sick”, “Tickling or tingling in the throat” or “Feeling of fullness in the stomach”, while those 65 years or older had

a high prevalence of “Feeling that something is stuck in the throat” (Figure 2).

Symptom improvement rate

The symptom improvement rate in patients with reflux-type symptoms and in those with ulcer- and dysmotility-type symptoms are shown in Figure 3. In those with reflux-type symptoms, improvement was achieved in 83–94% of patients at week 4. Almost the same improvement rates were seen at week 2, suggesting that omeprazole relieved symptoms early.

In patients with ulcer- and dysmotility-type symptoms, all symptoms except anorexia showed similar improvement to reflux-type: 71–86% of patients at week 2 and 84–94% at week 4. Improvement rates for anorexia at weeks 2 and 4 were 61% and 71%, respectively.

Symptom improvement rates at dosages of omeprazole 10 mg and 20 mg are shown in Table 4.

Fig. 3. Symptom improvement rate in patients with reflux-type symptoms (a) and ulcer- and dysmotility-like symptoms (b).

Table 4. Symptom improvement rate in each dosage at week 4

Symptoms	Improvement rate	
	10 mg daily	20 mg daily
Reflux-type symptoms		
Tickling or tingling in the throat	93.3% (14/15)	80.4% (37/46)
Feeling that sour contents are coming up from the stomach (regurgitation)	85.7% (24/28)	94.6% (88/93)
Feeling that something is stuck in the throat	86.7% (13/15)	94.2% (49/52)
Burning sensation in the chest (heartburn)	92.3% (24/26)	93.8% (90/96)
Ulcer- and dysmotility-type symptoms		
Pain in the stomach	90.0% (18/20)	83.6% (61/73)
fasting	80.0% (4/5)	82.1% (23/28)
after meal	90.0% (9/10)	90.0% (18/20)
Nausea or feeling sick	90.9% (10/11)	95.7% (66/69)
Heavy feeling in the stomach	95.2% (20/21)	89.9% (71/79)
Feeling of fullness in the stomach	80.0% (16/20)	90.0% (63/70)
Belching	84.2% (16/19)	83.3% (55/66)
No appetite (anorexia)	81.3% (13/16)	67.4% (31/46)

Table 5. Symptom complete relief rate in each dosage at week 4

Symptoms	Complete relief rate	
	10 mg daily	20 mg daily
Reflux-type symptoms		
Tickling or tingling in the throat	53.3% (8/15)	54.3% (25/46)
Feeling that sour contents are coming up from the stomach (regurgitation)	60.7% (17/28)	62.4% (58/93)
Feeling that something is stuck in the throat	53.3% (8/15)	63.5% (33/52)
Burning sensation in the chest (heartburn)	61.5% (16/26)	67.7% (65/96)
Ulcer- and dysmotility-type symptoms		
Pain in the stomach	35.0% (7/20)	52.1% (38/73)
fasting	40.0% (2/5)	42.9% (12/28)
after meal	50.0% (5/10)	70.0% (14/20)
Nausea or feeling sick	36.4% (4/11)	68.1% (47/69)
Heavy feeling in the stomach	38.1% (8/21)	53.2% (42/79)
Feeling of fullness in the stomach	35.0% (7/20)	55.7% (39/70)
Belching	42.1% (8/19)	45.5% (30/66)
No appetite (anorexia)	56.3% (9/16)	50.0% (23/46)

Complete symptom relief rate

Reflux-type symptoms were completely relieved in 53–66% of patients at week 4, while ulcer- and dysmotility-type symptoms were completely relieved in 48–63% of patients.

Complete symptom relief rates at dosages of omeprazole 10 mg and 20 mg are shown in Table 5. Complete symptom relief rates in ulcer- and dysmotility-type symptoms at week 4 after omeprazole 20 mg/day dosing is slightly higher than the rates after omeprazole 10 mg/day dosing, but a caution is necessary to interpret this result due to the smaller number of patients in 10 mg/day dosing group. In reflux-type symptoms, the complete relief rates were 53–68% in both dosages.

4. GSRS score

A total of 164 out of 221 patients were comparable for GSRS score at study entry, week 2 and week 4. GSRS total score and five symptom categorical scores are shown in Figure 4. GSRS total score at entry was 2.2 ± 0.7 (mean $\pm$ SD) and was significantly improved to 1.6 ± 0.6 at week 2 and 1.5 ± 0.5 at week 4 ($p < 0.01$). Reflux score, abdominal pain score and indigestion score were reduced by 1.0, 0.7 and 0.5 at week 2 respectively whereas smaller improvement was seen in diarrhea score (0.2) and constipation score (0.3). All categorical scores were

significantly improved after administration of omeprazole ($p < 0.01$).

Discussion

A large number of patients complain of upper abdominal symptoms in daily clinical practice in Japan. Approximately 30% of the general population experience upper abdominal symptoms at least once a week according to the Gastroenterology Surveillance Study [11] in 10 countries, including Japan. While this result included symptoms from patients with organic disease such as PU and gastroesophageal reflux disease, the prevalence of FD in the general population has been reported in other studies: 11.5–14.5% in Western countries [12] and 13% in Japan [13]. Hirakawa *et al.* suggested that the prevalence of non-ulcer dyspepsia, consisting of FD and reflux-like dyspepsia, was 17% among the Japanese population [14]. Thus, patients with upper abdominal symptoms are very common in Japan as well as in Western countries.

Patients with upper abdominal symptoms are commonly prescribed prokinetics in Japan, as acute gastritis or exacerbation of chronic gastritis is often the diagnosis, if organic disease is not found upon examination. Prokinetics

Fig. 4. Change in mean GRSRS score over time.

are recommended for the treatment of dysmotility-like dyspepsia [15], but a satisfactory effect is not always achieved [3, 4]. In other words, those patients who visit hospitals have rather pronounced symptoms and decreased QOL, nevertheless, their symptoms are not well controlled by the medications given in most cases. This causes patients to change hospitals with their uncontrolled symptoms and anxiety [16].

Symptom control and improvement of QOL are the purpose of the treatment for patients suffering from upper abdominal symptoms. In Western countries, especially in primary care, an empiric trial of PPIs is recommended for the management of dyspepsia [17]. Omeprazole has been shown to be an efficacious treatment option in this case [18]. However, US recommendations may not be applicable for Japanese clinical practice due to the popularization of endoscopy and high prevalence of gastric cancer, yet the proposed link between upper abdominal symptoms and acid is interesting.

In the present study, reflux-type symptoms (e.g. burning sensation in the chest) and ulcer- and dysmotility-type symptoms (e.g. heavy feeling or pain in the stomach) were seen at study entry in patients with RE. Ulcer- and dysmotility-type symptoms were observed in up to 62% of patients, while reflux-type symptoms were seen in approximately 70%. As presence of heartburn was not mandatory for patient selection in this study, it was estimated that approximately 30% of patients had a predominant symptom other than heartburn. Ulcer- and dysmotility-type symptoms are seen in a certain number of patients, and the mechanism of interaction with acid has been studied. As Lee *et al.* reported, increased gastric sensitivity to gastric distension due to duodenal acid exposure might cause the symptoms [19].

After omeprazole administration, almost all symptoms were improved by week 4 in approximately 90% of patients.

Similar improvement rates were achieved regardless of symptom types and dosage. The symptoms were completely resolved in 48–66% of patients. In a Canadian study in *H. pylori*-negative patients with dyspepsia, omeprazole showed superior symptom relief compared with ranitidine, cisapride and placebo [7]. Symptoms were improved or resolved by omeprazole treatment regardless of symptom types, suggesting that gastric acid is somewhat associated with upper abdominal symptoms and can be treated by PPIs.

QOL was measured by GRSRS in this study. Reflux score was the worst at study entry and at week 4, all scores were improved significantly compared to the baseline score. Both diarrhea and constipation scores were significantly reduced, improvement from baseline score was minimum. QOL in patients with RE is lower than that in patients with heart failure (mild) and angina pectoris [20]. It is known that QOL in patients with FD is also decreased [1, 2] and may be as low as patients with RE due to upper abdominal symptoms. Once symptoms are relieved by PPI treatment, improvement of QOL in patients with upper abdominal symptoms is expected.

The purpose of this study was to collect symptom information observed in patients with RE and to investigate the efficacy of omeprazole on the symptoms. Ulcer- and dysmotility-type symptoms such as “Heavy feeling in the stomach” and “Feeling of fullness in the stomach” in addition to the typical symptoms of RE were frequently reported in patients entered in the study. Symptoms were improved or completely resolved after treatment of omeprazole and QOL was also improved. Although this was the study in patients with RE, this result may suggest omeprazole can be effective for the treatment of upper abdominal symptoms such as ulcer- and dysmotility-type symptoms as well as reflux symptoms regardless of gastrointestinal lesion.

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