CURRENT THERAPEUTIC RESEARCH

VOLUME 67, NUMBER 1, JANUARY/FEBRUARY 2006

Postmarketing Surveillance of Rabeprazole in Upper Gastrointestinal Peptic Lesions in Japanese Patients with Coexisting Hepatic Disorders

Isao Makino, MD[1]; Kimihide Nakamura, MD[1]; Yoichi Sato, MD[1]; Yuzuru Sato, MD[2]; Shuichi Sezai, MD[2]; Yusei Ikeda, MD[3]; Wahei Shinmura, MD[3]; Hajime Watahiki, MD[4]; Hideaki Yamamoto, MD[4]; Yayuki Hioki, MD[4]; Masao Suzuki, MD[4]; Takashi Kumada, MD[5]; Takashi Honda, MD[5]; Tomoo Rikitoku, MD[5]; Yasuhiro Hisanaga, MD[5]; Hiroshi Fukui, MD[6]; Junichi Yamao, MD[6]; Hironaka Kawasaki, MD[7]; Akihide Hosoda, MD[7]; Morikazu Onji, MD[8]; Hidetaka Matsui, MD[8]; Michio Sata, MD[9]; Takuji Torimura, MD[9]; Kazuhiko Oho, MD[9]; Ryuichiro Maekawa, MD[10]; Yoshiyuki Takagi, MD[10]; Satoshi Shakado, MD[10]; Masafumi Nakayama, MD[10]; Kazuhisa Gondo, MD[11]; Hirofumi Fukushima, MD[12]; Taku Kusaba, MD[12]; Hirohito Tsubouchi, MD[13]; Katsuhiro Hayashi, MD[13]; Takeshi Hori, MD[13]; Yozo Iida, MD[14]; Kouki Yutoku, MD[14]; Noboru Maetani, MD[14]; Yoshitsugu Kubo, MD[14]; and Yoshifumi Miyata, MD[15]

[1]Second Department of Internal Medicine, Asahikawa Medical College, Hokkaido, Japan; [2]Division of Gastroenterology, Kanto Medical Center NTT EC, Tokyo, Japan; [3]Department of Internal Medicine, Tokyo-Kosei-nenkin Hospital, Tokyo, Japan; [4]Department of Gastroenterology, Seirei Mikatahara General Hospital, Shizuoka, Japan; [5]Department of Gastroenterology, Ogaki Municipal Hospital, Gifu, Japan; [6]Third Department of Internal Medicine, Nara Medical University, Nara, Japan; [7]Second Department of Internal Medicine, Faculty of Medicine, Tottori University, Tottori, Japan; [8]Third Department of Internal Medicine, Faculty of Medicine, Ehime University, Ehime, Japan; [9]Second Department of Medicine, Kurume University School of Medicine, Fukuoka, Japan; [10]Department of Internal Medicine, Social Insurance Tagawa Hospital, Fukuoka, Japan; [11]Department of Internal Medicine, Fukuoka Prefectural Yanagawa Hospital, Fukuoka, Japan; [12]Department of Internal Medicine, Fukuokaken Saiseikai Futsukaichi Hospital, Fukuoka, Japan; [13]Department of Internal Medicine, Miyazaki Medical College Hospital, Miyazaki, Japan; [14]Department of Gastroenterology, Kokura Memorial Hospital, Fukuoka, Japan; and [15]Department of Internal Medicine, Chubu Hospital, Miyazaki, Japan

ABSTRACT

Background: Many Japanese patients with hepatic disorders confirmed on diagnostic imaging and coexisting upper gastrointestinal (GI) peptic lesions receive treatment with proton pump inhibitors. Some pharmacotherapies used to treat peptic ulcers have been associated with adverse drug reactions (ADRs), including elevated liver enzyme levels.

Accepted for publication December 27, 2005.
Reproduction in whole or part is not permitted.

doi:10.1016/j.curtheres.2006.02.003
0011-393X/06/$19.00

Objective: The aim of this study was to determine the tolerability and effectiveness of rabeprazole sodium in treating peptic lesions in patients with coexisting hepatic disorders.

Methods: This open-label, practice-based, postmarketing surveillance investigation was conducted at 15 centers across Japan. Male and female patients aged ≥18 years with peptic lesions confirmed on upper GI endoscopy and with underlying hepatic disease were enrolled. Patients were randomly assigned to receive rabeprazole 10 or 20 mg PO (tablet) QD after a meal for up to 8 weeks. Tolerability was assessed using monitoring of the incidence of ADRs determined by direct patient questioning, spontaneous reporting, and laboratory assessment. All patients who received at least 1 dose of study drug were included in the tolerability assessment. Effectiveness was assessed at baseline and study end using the rates of achievement of improvement on endoscopy, relief of subjective/objective symptoms (rates of improvement in epigastric pain and heartburn), and global improvement. The effectiveness analysis included all patients with complete data before and after treatment. Subanalyses were conducted to determine the effectiveness of drug by identification of the proportion of patients with coexisting hepatic disorders (cirrhosis, chronic hepatitis, and other hepatic diseases [eg, alcoholic hepatitis, fatty liver]) and by peptic lesion (gastric ulcer, duodenal ulcer, stomal ulcer, and reflux esophagitis) who achieved improvement.

Results: A total of 114 patients were enrolled; 108 patients were included in the tolerability analysis (81 men, 27 women; mean age, 59.9 years; 10-mg dose, 90 patients; 20-mg dose, 18 patients) and 98 patients were included in the analysis of effectiveness. Twenty-one ADRs occurred in 11 (10.2%) patients. Serious ADRs occurred in 2 patients (elevated bilirubin level and hepatic encephalopathy, 1 patient each). Administration of rabeprazole was discontinued in 5 patients due to the occurrence of the following ADRs: constipation (1 patient); epigastric pain (1); dyslalia, disorientation, tremor, sleep disorder, and hepatic encephalopathy (1); diarrhea (1); and elevated alkaline phosphatase and γ-glutamyl transpeptidase levels (1). On endoscopy, the proportion of patients achieving improvement with either dose was 30/33 (90.9%). The relief rates assessed using subjective symptoms were 47/55 (85.5%) and 47/56 (83.9%) for epigastric pain and heartburn, respectively. The proportion of patients achieving global improvement with either dose was 80/98 (81.6%) patients (49/62 [79.0%] for cirrhosis, 11/16 [68.8%] for chronic hepatitis, and 20/20 [100.0%] for other hepatic diseases [alcoholic hepatitis, fatty liver]).

Conclusion: In this study in Japanese patients with hepatic disorders, rabeprazole was well tolerated and appeared effective for the treatment of upper GI peptic lesions. (*Curr Ther Res Clin Exp.* 2006;67:1–20)

Key words: rabeprazole, hepatic disorders, cirrhosis, chronic hepatitis, upper gastrointestinal lesions, gastric ulcer, duodenal ulcer, reflux esophagitis, stomal ulcer.

INTRODUCTION

Hepatic disorders are broadly classified based on progression to hepatitis (acute or chronic), cirrhosis, and hepatocellular carcinoma.[1] *Cirrhosis* is subclassified as *compensated cirrhosis* and *decompensated cirrhosis* (hepatic insufficiency), depending on the presence or absence of overt jaundice, ascites, edema, and impairment of consciousness.[1] A cirrhotic liver (during decompensated stage) has reduced function, with particular reductions in drug-metabolizing activity and compromised activity to synthesize proteins, such as albumin, possibly leading to increased unbound and total drug concentrations in the blood.[2] Hepatic disorders cause reduced hepatic function and various complications (including subjective symptoms). Major complications of severe hepatic disease include general malaise, fatigue, palmar erythema, spider angioma, purpura, jaundice, ascites, esophageal varices, and hepatic encephalopathy.[3]

Approximately 10% to 20% of patients with hepatic disorders (including cirrhosis and chronic hepatitis) develop upper gastrointestinal (GI) peptic lesions.[4,5] Reductions in gastric mucosal defensive factors[6] and altered gastric acid secretion[7] have been associated with the development of peptic lesions in patients with hepatic disease. In these patients, peptic lesions are typically treated in the same manner as peptic ulcers uncomplicated by hepatic disease, using agents such as gastric secretion suppressants[8] and mucosal defensive factor enhancers.[9] Proton pump inhibitors (PPIs) are commonly used for the treatment of peptic lesions. However, despite their widespread use, PPIs have been associated with adverse drug reactions (ADRs) (incidence, ~1%–5%), including elevated liver enzyme levels.[10,11]

Patients with cirrhosis experience a high frequency of GI lesions caused by congested blood circulation in the gastric mucosa,[12–14] decreased prostaglandin E_2 levels, decreased membrane potential in the gastric mucosa,[15,16] and excess secretion of gastric juice (during compensated cirrhosis stage).[17] According to study results reported at the 30th Annual Conference of the Japanese Gastroenterological Endoscopy Society,[18] patients with cirrhosis experience peptic complication at a higher rate compared with healthy individuals, with the incidence being 20% to 30% for redness and erosion, 15% to 20% for gastric ulcer, and ~10% for duodenal ulcer. These peptic lesions are usually treated with various mucosal defensive factor enhancers, prostaglandins, histamine-H_2 receptor antagonists, and PPIs. PPIs are often used for the treatment of intractable gastric/duodenal ulcers in cirrhotic patients.

One PPI, rabeprazole sodium, was approved by the US Food and Drug Administration in 1999 for the short-term (4–8 weeks) treatment of erosive or ulcerative gastroesophageal reflex disease (GERD); symptomatic GERD; maintaining healing in patients with GERD; healing and symptomatic relief of duodenal ulcers; long-term treatment of pathologic hypersecretory conditions, including Zollinger-Ellison syndrome; and the eradication of *Helicobacter pylori* in combination with amoxicillin and clarithromycin. Rabeprazole has been found to be efficacious in the treatment of gastric ulcer, duodenal ulcer, and

GERD.[19,20] However, because many antiulcer drugs, including rabeprazole,[21] are metabolized in the liver, and because liver enzyme activity might be reduced in patients with hepatic diseases, ADRs might occur at a higher rate in these patients compared with healthy individuals. In the livers of patients with normal hepatic function, rabeprazole is rapidly metabolized after being absorbed from the digestive tract via the first-pass effect. In contrast, in patients with hepatic disease, administration of rabeprazole tablets has been reported to cause a prolonged $t_{1/2}$, decreased total body clearance,[22] and increased aminotransferase levels.[19,23] Due to the hepatic metabolism of PPIs, including rabeprazole, the debilitated state of patients with hepatic disease, and the possibility of ADRs,[19,21,23] any drug used in patients with complicated hepatic disease must be scrutinized.

Based on a MEDLINE search for literature concerning rabeprazole use (key terms: *rabeprazole*, *peptic lesion*, and *hepatic disease*; years: 1997–2005), the tolerability and effectiveness of this drug in patients with peptic lesions and underlying hepatic disease in routine clinical practice has not yet been clarified. We conducted the present survey to assess the tolerability and effectiveness of rabeprazole in patients with upper GI peptic lesions and coexisting hepatic disorders in routine clinical practice in Japan.

PATIENTS AND METHODS

This multicenter, open-label, practice-based, postmarketing surveillance investigation was conducted at 15 medical institutions across Japan. The study protocol was derived according to the principles of Good Post-Marketing Surveillance Practice.[24] Institutional review board approval of the study protocol was obtained from each participating institution.

Inclusion and Exclusion Criteria

Recruiting was performed using a central registration method to enroll patients who were confirmed as eligible using routine medical examination, endoscopy, and histopathology from June 1998 to July 1999. Male and female patients aged ≥18 years with endoscopically confirmed peptic lesions (including gastric ulcer, duodenal ulcer, stomal ulcer, and reflux esophagitis) and coexisting hepatic disease were eligible for enrollment. Patients receiving rabeprazole treatment or unable to receive drugs orally due to dysphagia or encephalopathy were excluded. Pregnant or breastfeeding patients were excluded. Before initiation of rabeprazole treatment, written informed consent was obtained from each patient.

Study Drug Administration

Patients received rabeprazole 10 or 20 mg PO (enteric-coated tablet) QD after a meal for 6 weeks for the treatment of duodenal ulcer, or 8 weeks for gastric ulcer, stomal ulcer, and/or reflux esophagitis. During the treatment period, if improvement (based on the investigator's judgment using endoscopic findings and subjective symptoms) was not achieved, the dose could be increased to 20 mg QD.

Because this study was conducted in the routine clinical practice setting, no restriction was placed on concomitant drugs. If concomitant drugs were used during the treatment period, the drug, dose, route of administration, and treatment duration were recorded in each patient's case-report form.

Tolerability Assessment

Patients underwent the following laboratory assessments before and after rabeprazole treatment: hematology and biochemistry (red and white blood cell counts; differentials [basophils, eosinophils, neutrophils, lymphocytes, and monocytes]; platelet count; hemoglobin concentration; hematocrit; and serum levels of aspartate and alanine aminotransferases, γ-glutamyl transpeptidase [γ-GTP], lactate dehydrogenase, total bilirubin, albumin, C-reactive protein, total cholesterol [TC], triglycerides [TG], blood urea nitrogen, serum creatinine, and prothrombin time).

All medically undesirable symptoms/findings that occurred after the start of treatment with rabeprazole were regarded as adverse events (AEs), and classified as ADRs if a causal relationship with rabeprazole could not be ruled out. Symptoms/findings and abnormal laboratory values were compared separately. Effects of demographic and clinical characteristics of patients on the occurrence of ADRs were investigated. Direct patient questioning and spontaneous reporting were also used to assess tolerability.

Effectiveness Assessment

Improvement on Endoscopy

Endoscopic examinations were performed before (baseline) and after (in a subset of patients, depending on their condition) the treatment period. Endoscopic findings were assessed according to the stage classification of Sakita and Miwa[25] for gastric, duodenal, and stomal ulcer, and reflux esophagitis according to the Los Angeles Classification,[26] using the following scale: for gastric, duodenal, or stomal ulcer: 1 = stage A1 (active ulcer); 2 = stage A2 (active ulcer); 3 = stage H1 (partially healed); 4 = stage H2 (partially healed); 5 = stage S1 (completely healed); and 6 = stage S2 (completely healed); for reflux esophagitis: 1 = grade D (mucosal breaks that involve ≥75% of the esophageal circumference); 2 = grade C (mucosal breaks that extend between the tops of 2 or more mucosal folds but that involve <75% of the esophageal circumference); 3 = grade B (≥1 mucosal breaks >5 mm); 4 = grade A (≥1 mucosal breaks ≤5 mm); and 5 = grade O (completely healed).

Symptom Improvement

Severity of subjective symptoms such as epigastric pain and heartburn was monitored before and after treatment. The severity of symptoms was assessed on a 4-point Likert scale (0 = none [–]; 1 = mild, occasionally symptomatic [±]; 2 = moderate, symptomatic [+]; and 3 = symptomatic and painful [++]).

Global Improvement Rating Scale

At the end of the treatment period, the effectiveness of rabeprazole was assessed using a global improvement rating, based on the changes over time in endoscopic findings and subjective symptoms, using a 5-point scale (0 = unassessable; 1 = aggravated; 2 = unchanged; 3 = slightly improved; and 4 = improved).

Subanalysis

Subanalyses were conducted to determine the effectiveness of rabeprazole by calculating the proportions of patients with coexisting hepatic disorders (cirrhosis [including hepatocellular carcinoma], chronic hepatitis, and other hepatic diseases [alcoholic hepatitis, fatty liver]) and by peptic lesion (gastric, duodenal, and stomal ulcer; and reflux esophagitis) who achieved improvement.

Statistical Analysis

The tolerability analysis comprised all patients who received at least 1 dose of study drug. For laboratory values, all patients with complete data before and after treatment were included in the tolerability analysis. ADRs were assessed with 90% CIs of the incidence by separate calculation for symptoms and laboratory abnormalities. The analysis was performed using the Fisher exact test for variables with 2 strata and by χ^2 test for those with ≥3 strata. For ADRs occurring in >5 patients, data were to be analyzed using the Fisher exact test regardless of the number of strata. The analysis was carried out with significance level of 5% (2-sided); no adjustment was attempted for multiplicity.

The effectiveness analysis included all patients with complete data before and after treatment. Changes in endoscopic scores before and after treatment were compared using the Wilcoxon signed rank test. The rate (95% CI) of complete healing (stage S1 or S2) at treatment completion was calculated. The rate (95% CI) of patients with a symptom rating of "none (–)" at treatment completion was calculated. Patients with no symptoms at treatment initiation were excluded from the analysis. Changes in subjective symptom scores before and after treatment were compared using the Wilcoxon signed rank test. The rates (95% CI) of global improvement or aggravation (worsening of peptic lesions) were calculated. F distribution was used to calculate CI.

RESULTS

One hundred fourteen patients were enrolled in the study (tolerability analysis, 108 patients; effectiveness analysis, 98 patients). Six patients were excluded from all analyses due to loss to follow-up (2 patients), protocol violations (3), and unavailable data (1).

Tolerability

Table I shows the demographic and clinical characteristics of the patients included in the tolerability analysis. Most patients were men (81 [75.0%]); the

Table I. Demographic and clinical characteristics of the study patients (tolerability population; n = 108).*

Item	No. (%) of Patients
Age group	
≤39 y	7 (6.5)
40–64 y	59 (54.6)
≥65 y	42 (38.9)
Patient status	
Outpatients	52 (48.1)
Inpatients	27 (25.0)
In- → outpatients	28 (25.9)
Out- → inpatients	1 (0.9)
Sex	
Male	81 (75.0)
Female	27 (25.0)
Digestive tract disease	
Gastric ulcer	47 (43.5)
Reflux esophagitis	38 (35.2)
Duodenal ulcer	21 (19.4)
Stomal ulcer	2 (1.9)
Severity of digestive tract disease	
Mild	46 (42.6)
Moderate	50 (46.3)
Severe	12 (11.1)
Relapse history	
First occurrence	70 (64.8)
Relapse	32 (29.6)
Unknown	6 (5.6)
Hepatic disorder	
Cirrhosis†	70 (64.8)
Chronic hepatitis	17 (15.7)
Other	21 (19.4)
Complication	
Yes	67 (62.0)
No	41 (38.0)
Allergic diathesis	
Yes	4 (3.7)
No	104 (96.3)

(continued)

Table I. (Continued)

Item	No. (%) of Patients
Previous treatment with antiulcer agents	
Yes	69 (63.9)
No	39 (36.1)
Concomitant drugs	
Yes	93 (86.1)
No	15 (13.9)
Rabeprazole dose	
10 mg	89 (82.4)
20 mg	17 (15.7)
10 → 20 mg	1 (0.9)
20 → 10 mg	1 (0.9)
Treatment duration‡	
≤14 d	15 (13.9)
15–28 d	11 (10.2)
29–42 d	20 (18.5)
43–56 d	39 (36.1)
≥57 d	23 (21.3)
Baseline hepatic function§	
Total bilirubin	
Normal (<1.6 mg/dL)	76 (70.4)
Grade 1 (1.6–<3.0 mg/dL)	18 (16.7)
Grade 2 or 3 (≥3.0 mg/dL)	5 (4.6)
Not determined	9 (8.3)
AST	
Normal (<50 U/L)	48 (44.4)
Grade 1 (50–<100 U/L)	40 (37.0)
Grade 2 or 3 (≥100 U/L)	13 (12.0)
Not determined	7 (6.5)
ALT	
Normal (<50 U/L)	57 (52.8)
Grade 1 (50–<100 U/L)	31 (28.7)
Grade 2 or 3 (≥100 U/L)	13 (12.0)
Not determined	7 (6.5)
Al-P	
Normal	60 (55.6)
Grade 1 (1.25–<2.5 × ULN)	31 (28.7)
Grade 2 or 3 (≥2.5 × ULN)	6 (5.6)
Not determined	11 (10.2)

(continued)

Table I. (Continued)

Item	No. (%) of Patients
γ-GTP	
Normal	56 (51.9)
Grade 1 (1.5–<2.5 × ULN)	19 (17.6)
Grade 2 or 3 (≥2.5 × ULN)	22 (20.4)
Not determined	11 (10.2)
LDH	
Normal	90 (83.3)
Abnormal (≥1.5 × ULN)	6 (5.6)
Not determined	12 (11.1)
Platelet count	
Normal (>100 × 10^3 cells/μL)	58 (53.7)
Grade 1 (75–100 × 10^3 cells/μL)	18 (16.7)
Grade 2 or 3 (<75 × 10^3 cells/μL)	22 (20.4)
Not determined	10 (9.3)
Albumin	
Normal	51 (47.2)
Grade 1 (1.5–<2.5 × ULN)	23 (21.3)
Grade 2 or 3 (≥2.5 × ULN)	16 (14.8)
Not determined	18 (16.7)

AST = aspartate aminotransferase; ALT = alanine aminotransferase; Al-P = alkaline phosphatase; ULN = upper limit of normal; γ-GTP = γ-glutamyl transpeptidase; LDH = lactate dehydrogenase.
*Percentages may not add to 100% due to rounding.
†Includes hepatocellular carcinoma.
‡For patients with adverse drug reactions (ADRs), data were collected until the date of the onset of the ADR.
§Classification based on the Criteria for Severity Grading of ADRs[27] and the criteria established for the survey of use status of rabeprazole tablets.

mean age was 59.9 years. Patients aged 40 to 64 years accounted for the largest proportion (59 [54.6%]), followed by those aged ≥65 years (42 [38.9%]). Patients with cirrhosis (including hepatocellular carcinoma) accounted for the majority (70 [64.8%]), followed by those with chronic hepatitis (17 [15.7%]).

Rabeprazole tablets were administered at 10 mg/d to 90 (83.3%) patients and at 20 mg/d to 18 (16.7%) patients.

Table II lists ADRs by patient. Of 108 patients, 11 (10.2%) (90% CI, 5.8%–16.3%) experienced 21 ADRs, as follows: metabolism and nutritional disorders in 3 patients, 5 events (elevated alkaline phosphatase level [3], elevated serum TG level [1], elevated serum TC or low-density lipoprotein cholesterol [LDL-C] level [1]); hepatic and biliary system disorders, 5 patients, 5 events

Table II. Adverse drug reactions (ADRs) with up to 8 weeks of treatment with rabeprazole 10 or 20 mg/d in patients with upper gastrointestinal peptic lesions complicated by underlying hepatic disease (n = 11*).

Age/Sex	Primary Disease	Digestive Tract Disease	Complications	ADR	Day of Onset	Outcome	Causal Relationship
75/F	Cirrhosis	Gastric ulcer	Gastric varices	Serious ↑bilirubin†	30	Remitted	Possibly related
67/M	Alcoholic cirrhosis	Gastric ulcer	Diabetes mellitus	Loose stools	1	Recovered	Related
63/F‡	Autoimmune hepatitis	Reflux esophagitis	Rheumatoid arthritis	Loose stools, constipation	1, 7	Recovered	Related
63/M	Cirrhosis type C	Reflux esophagitis	Diabetes mellitus	↑Al-P,§ ↑γ-GTP‖	27	Remitted	Possibly related
33/F‡	Chronic hepatitis C	Reflux esophagitis	None	Epigastric pain (aggravated)	2	Recovered	Possibly related
67/M‡¶	Cirrhosis	Duodenal ulcer	Esophageal varices	Severe dyslalia, disorientation, tremor, sleep disorder, and hepatic encephalopathy	22	Recovered	Related
67/F	Cirrhosis	Gastric ulcer	Bursitis of ankle	Purpura	6	Recovered	Probably related
44/M	Cirrhosis type B	Gastric ulcer	None	↑Al-P, ↑γ-GTP, ↑TC,# and ↑TG**	57	Unknown	Probably related
63/F‡	Cirrhosis	Gastric ulcer	Diabetes mellitus	Diarrhea	3	Recovered	Possibly related
72/M‡	Cirrhosis	Reflux esophagitis	Lung carcinoma	↑Al-P, ↑γ-GTP	11	Recovered	Possibly related
76/M	Cirrhosis type C	Reflux esophagitis	Depression	Eosinophilia	28	Unknown	Probably related

F = female; M = male; Al-P = alkaline phosphatase; γ-GTP = γ-glutamyl transpeptidase; TC = total cholesterol; TG = triglycerides.

*All patients were receiving the 10-mg dose.

†↑Bilirubin = ≥4.18 mg/dL.

‡Study drug was discontinued due to ADR in this patient, and this patient was withdrawn from the study.

§↑Al-P = ≥776 IU/mL.

‖↑γ-GTP = ≥124 IU/L.

¶This patient received treatment for ADRs.

#↑TC = 252 mg/dL.

**↑TG = 184 mg/dL.

(elevated γ-GTP level [3], elevated bilirubin level [1; serious], hepatic encephalopathy [1]); gastrointestinal system disorders, 4 patients, 5 events (loose stools [2], constipation [1], diarrhea [1], and epigastric pain [1]); central and peripheral nervous system disorders, 1 patient, 3 events (disorientation, dyslalia, and tremor [1 each]); leukocyte and reticuloendothelial system disorders, 1 patient, 1 event (eosinophilia); psychiatric disorder, 1 patient, 1 event (sleep disorder); and vascular (extracardiac) system disorder, 1 patient, 1 event (purpura). Five patients were counted in multiple categories, for a total of 16 events. Among the ADRs, 6 serious reactions were observed in 2 patients, 1 with elevated bilirubin and 1 with dyslalia, disorientation, tremor, sleep disorder, and hepatic encephalopathy. The outcome in these 2 patients with cirrhosis and hepatocellular carcinoma was recovery (dyslalia, disorientation, tremor, sleep disorder, and hepatic encephalopathy) or remission (elevated bilirubin) following the discontinuation of rabeprazole.

The outcomes of the 21 ADRs were recovery or remission in 16 patients and unknown due to loss to follow-up in 5 (elevated levels of alkaline phosphatase; γ-GTP; serum TG, TC, and LDL-C; and eosinophilia).

Administration of rabeprazole was discontinued in 5 patients due to the occurrence of the following ADRs: constipation (day 7); epigastric pain (day 2); dyslalia, disorientation, tremor, sleep disorder, and hepatic encephalopathy (day 22); diarrhea (day 3); and elevated alkaline phosphatase and γ-GTP levels (day 11).

Five ADRs in 1 patient required treatment (dyslalia, disorientation, tremor, sleep disorder, and hepatic encephalopathy); these ADRs were treated successfully with flumazenil. One patient was an asymptomatic carrier of hepatitis B virus in whom duodenal ulcer and mild anemia developed on day 45 of treatment with rabeprazole 10 mg/d. This patient was excluded from the tolerability and effectiveness analyses. The anemia was treated successfully with sodium ferrous citrate.

The incidence of symptoms/findings was 6/108 (5.6%) (90% CI, 2.45%–10.67%), and the incidence of abnormal laboratory values was 5/108 (4.6%) (90% CI, 1.84%–9.49%).

Some laboratory values deviated from the normal range, but no marked changes from baseline were observed in any patient. Laboratory values considered ADRs were as follows: hematologic values, 1 patient, 1 event (mild eosinophilia); and liver function values, 4 patients, 4 events (mild elevated γ-GTP level [3] and serious elevated bilirubin level [1]). Among them, outcomes of the elevated γ-GTP level and eosinophilia were unknown due to loss to follow-up. All other abnormal laboratory values returned to normal or were improved after study completion.

The incidence of ADRs was significantly higher in inpatients compared with outpatients (6 [22.2%] vs 5 [9.6%] patients; $P < 0.045$) and in patients with a treatment duration ≤28 days compared with those who received treatment for >28 days (9 [34.6%] vs 2 [2.4%] patients; $P < 0.001$). No other demographic and

clinical characteristics were found to have a significant effect on the incidence of ADRs.

Of the 70 (64.8%) patients with cirrhosis (including hepatocellular carcinoma), 40 (57.1%) patients had been treated with concomitant drugs to prevent ascites and/or impairment of consciousness and were thus considered to have decompensated cirrhosis. Two of them also had received anticancer agents (epirubicin hydrochloride, mitomycin C) to treat hepatocellular carcinoma. Of the 11/70 (15.7%) patients who experienced ADRs, 9 had cirrhosis.

Effectiveness

The demographic and clinical characteristics of the 98 patients included in the effectiveness analysis are shown in **Table III**. Patients aged 40 to 64 years accounted for the largest proportion (54 [55.1%]) and male patients were predominant (74 [75.5%]). The prevalences of lesions in the 98 patients were as follows: gastric ulcer, 45 (45.9%) patients; duodenal ulcer, 17 (17.3%); reflux esophagitis, 34 (34.7%); and stomal ulcer, 2 (2.0%). The prevalences of preexisting hepatic disorders were: cirrhosis, 62 (63.3%) patients (including 20 patients with hepatocellular carcinoma); chronic hepatitis, 16 (16.3%); and other, 20 (20.4%). Rabeprazole was administered at 10 mg/d to 80 (81.6%) patients and at 20 mg/d to 16 (16.3%) patients. The dose was changed in 2 (2.0%) patients during the course of the treatment.

Improvement on Endoscopy

Of the 98 patients included in the analysis of effectiveness, 33 (33.7%) patients with complete endoscopic data before and after treatment with 10 or 20 mg were eligible for analysis.

Endoscopic findings showed improvement in 30/33 (90.9%) patients. Changes in endoscopic assessment score before and after treatment are shown in **Tables IV** and **V**. The healing rates of peptic lesions were: gastric ulcer, 14/18 (77.8% [95% CI, 52.4%–93.6%]); duodenal ulcer, 3/5 (60.0% [95% CI, 14.7%–94.7%]) (**Table IV**); and reflux esophagitis, 4/9 (44.4% [95% CI, 13.7%–78.8%]) (**Table V**). Stratification by peptic lesion found significantly improved endoscopic scores for gastric ulcer and reflux esophagitis (**Table VI**). Of the 3 (9.1%) patients without endoscopic improvement, 1 had gastric and duodenal ulcers complicated by cirrhosis and hepatic encephalopathy (this patient was receiving concomitant NSAIDs), and 2 had reflux esophagitis and cirrhosis.

Symptom Relief Rates

The predominant symptoms were heartburn (56 [57.1%]) and epigastric pain (55 [56.1%]). Both of these symptoms were significantly improved with rabeprazole use.

The relief rates of epigastric pain and heartburn were 47/55 (85.5%) and 47/56 (83.9%), respectively. Improvement rates of epigastric pain and heartburn

Table III. Demographic and clinical characteristics of the study patients (effectiveness population; n = 98).

Characteristic	No. (%) of Patients
Age group	
≤39 y	7 (7.1)
40–64 y	54 (55.1)
≥65 y	37 (37.8)
Patient status	
Outpatients	46 (46.9)
In- → outpatients	27 (27.6)
Inpatients	24 (24.5)
Out- → inpatients	1 (1.0)
Sex	
Male	74 (75.5)
Female	24 (24.5)
Digestive tract disease	
Gastric ulcer	45 (45.9)
Reflux esophagitis	34 (34.7)
Duodenal ulcer	17 (17.3)
Stomal ulcer	2 (2.0)
Severity	
Mild	41 (41.8)
Moderate	47 (48.0)
Severe	10 (10.2)
Relapse history	
First occurrence	65 (66.3)
Relapse	28 (28.6)
Unknown	5 (5.1)
Hepatic disorder	
Cirrhosis*	62 (63.3)
Chronic hepatitis	16 (16.3)
Other	20 (20.4)
Other complication†	
Yes	61 (62.2)
No	37 (37.8)
Previous treatment with anti-ulcer agents (all categories)	
Yes	64 (65.3)
No	34 (34.7)
Concomitant drugs	
Yes	84 (85.7)
No	14 (14.3)

(continued)

Table III. (Continued)

Characteristic	No. (%) of Patients
Rabeprazole dose‡	
10 mg	80 (81.6)
20 mg	16 (16.3)
10 mg → 20 mg	1 (1.0)
20 mg → 10 mg	1 (1.0)
Treatment duration	
≤14 d	9 (9.2)
15–28 d	11 (11.2)
29–42 d	17 (17.4)
43–56 d	40 (40.8)
≥57 d	21 (21.4)

*Includes 20 patients with hepatocellular carcinoma.
†Includes esophageal varices, hypertension, and diabetes mellitus.
‡Percentages do not total 100% due to rounding.

Table IV. Patients with healed ulcers on endoscopy after up to 8 weeks of treatment with rabeprazole 10 or 20 mg/d in patients with upper gastrointestinal peptic lesions complicated by underlying hepatic disease (effectiveness population; n = 98).

Ulcer Type/ Baseline Stage*	n	Posttreatment Ulcer Stage*				
		A2	H1	H2	S1	S2
Gastric†						
A1	7	0	1	0	4	2
A2	8	1	1	1	3	2
H1	2	0	0	0	1	1
H2	1	0	0	0	0	1
Duodenal†						
A1	3	–	0	1	2	0
A2	2	–	1	0	0	1

*Endoscopic findings were assessed according to the stage classification of Sakita and Miwa[25] for gastric, duodenal, and stomal ulcer, and reflux esophagitis according to the Los Angeles Classification,[26] using the following scale: 1 = stage A1 (active ulcer); 2 = stage A2 (active ulcer); 3 = stage H1 (partially healed); 4 = stage H2 (partially healed); 5 = stage S1 (completely healed); and 6 = stage S2 (completely healed).
†Endoscopic healing rate (95% CI) = (No. of patients with disease improved to stage S1 or S2)/(No. of patients eligible for analysis) × 100 = 77.8% (52.4%–93.6%) (gastric ulcer) and 60.0% (14.7%–94.7%) (duodenal ulcer).

Table V. Patients with healed reflux esophagitis on endoscopy after up to 8 weeks of treatment with rabeprazole 10 or 20 mg/d in patients with upper gastrointestinal peptic lesions complicated by underlying hepatic disease (effectiveness population; n = 98).*

Baseline MLAC Grade†	n	Posttreatment MLAC Grade†			
		C	B	A	D
D	3	1	0	0	2
C	2	0	0	2	0
B	3	0	2	0	1
A	1	0	0	0	1

MLAC = Modified Los Angeles classification.
*Endoscopic healing rate (No. of patients with disease improved to grade O/No. of patients eligible for analysis) × 100 = 44.4% (95% CI, 13.7%–78.8%).
†MLAC[26]: 1 = grade D (mucosal breaks that involve ≥75% of the esophageal circumference); 2 = grade C (mucosal breaks that extend between the tops of ≥2 mucosal folds but that involve <75% of the esophageal circumference); 3 = grade B (≥1 mucosal breaks >5 mm); 4 = grade A (≥1 mucosal breaks ≤5 mm); and 5 = grade O (completely healed).

Table VI. Changes in endoscopic scores before and after treatment with rabeprazole 10 or 20 mg/d for up to 8 weeks in patients with upper gastrointestinal peptic lesions complicated by underlying hepatic disease (effectiveness population; n = 98). Values are no. of patients.

Disease	Change in Score*					
	0	+1	+2	+3	+4	+5
Gastric ulcer	1	1	4	4	6	2
Duodenal ulcer	–	1	–	1	3	–
Stomal ulcer	–	–	–	1	–	–
Reflux esophagitis	2	2	3	–	2	–
All diseases	3	4	7	6	11	2

*The larger the change in the score in the plus direction, the larger the extent of the improvement.

combined were 63/80 (78.8%) and 15/16 (93.8%) in the 10- and 20-mg/d groups, respectively. The rates of epigastric pain relief were 35/43 (81.4%) and 10/10 (100%) in the 10- and 20-mg/d groups, respectively. The heartburn relief rates were 38/47 (80.9%) and 9/9 (100%) in the 10- and 20-mg/d groups, respectively.

The improvement rates by peptic lesion were as follows: gastric ulcer, 36/45 (80.0%); duodenal ulcer, 15/17 (88.2%); stomal ulcer, 2/2 (100.0%); and reflux esophagitis, 27/34 (79.4%).

The improvement rates by preexisting hepatic disorders were as follows: cirrhosis (including hepatocellular carcinoma), 49/62 (79.0%); chronic hepatitis, 11/16 (68.8%); and other hepatic diseases (alcoholic hepatitis, fatty liver), 20/20 (100%).

Global Improvement Rating

Of 98 patients, 80 (81.6%) (95% CI, 72.5%–88.7%) achieved improvement, 16 (16.3%) achieved slight improvement, and 2 (2.0%) were considered nonassessable because of the short duration of treatment or insufficient data available for assessment. None of the patients experienced aggravated peptic lesion (95% CI, 0%–0.4%).

Improvement rates by underlying hepatic disease were as follows: cirrhosis (including hepatocellular carcinoma), 49/62 (79.0%); chronic hepatitis, 11/16 (68.8%); and other hepatic disorders (alcoholic hepatitis, fatty liver), 20/20 (100.0%). These differences were not statistically significant. No other demographic or clinical characteristics were found to affect the improvement rate (**Table VII**).

DISCUSSION

Suzuki et al[3] reported that the rates of cirrhosis complicated by spider angioma, ascites, esophageal varices (stage II or more), and hepatic encephalopathy were 45.0%, 30.8%, 46.3%, and 15.6%, respectively. However, in our study, these complications were classified as ADRs if the onset was during rabeprazole treatment (as in 1 patient with underlying cirrhosis who experienced purpura and hepatic encephalopathy).

Of the 108 patients included in the tolerability analysis, 10.2% of patients experienced 21 ADRs. When tolerability results obtained in the present survey were compared with those obtained during the clinical development of rabeprazole (N = 1244),[28] the incidences of adverse symptoms and abnormal laboratory values observed were 1.8% (90% CI, 1.2%–2.5%) and 6.6% (90% CI, 5.28%–8.12%), respectively, compared with 5.6% (90% CI, 2.5%–10.7%) and 4.6% (90% CI, 1.8%–9.5%) in the present study.

Investigation of the association between baseline demographic and clinical characteristics and the incidence of ADRs revealed higher incidences observed in inpatients and in those who received short-term treatment. The higher incidence of ADRs observed in hospitalized patients suggests that the frequency is

Table VII. Global improvement ratings after up to 8 weeks of treatment with rabeprazole 10 or 20 mg/d in patients with upper gastrointestinal peptic lesions complicated by underlying hepatic disease (effectiveness population; n = 98). Values are no. (%) of patients.

Lesion or Disorder	n	Improved	Slightly Improved	Unchanged	Aggravated/ Worsened	Unable to Assess
Peptic lesions						
Gastric ulcer	45	36 (80.0)	8 (17.8)	0	0	1 (2.2)
Duodenal ulcer	17	15 (88.2)	2 (11.8)	0	0	0
Stomal ulcer	2	2 (100.0)	0	0	0	0
Reflux esophagitis	34	27 (79.4)	6 (17.6)	0	0	1 (2.9)
Diagnosis of hepatic disorder						
Cirrhosis	62	49 (79.0)	12 (19.4)	0	0	1 (1.6)
Chronic hepatitis	16	11 (68.8)	4 (25.0)	0	0	1 (6.3)
Other*	20	20 (100.0)	0	0	0	0
Total	98	80 (81.6)	16 (16.3)	0	0	2 (2.0)
		(95% CI, 72.5%–88.7%)			(95% CI, 0%–0.4%)	

*Includes fatty liver, autoimmune hepatitis.

associated with more severe hepatic disorders: 59.3% inpatients in the present survey had decompensated cirrhosis, compared with 19.2% outpatients.

Improvement on endoscopy was found in 90.9% patients ($P < 0.001$). Of the 3 patients without improvement, all had cirrhosis and 1 was receiving concomitant NSAIDs. The patient receiving NSAIDs showed improvement in subjective symptoms during treatment with rabeprazole, but the lack of endoscopic improvement could have been due to NSAID use. Subjective symptoms resolved during treatment in 1 patient with reflux esophagitis who had type C cirrhosis complicated by depression and hepatocellular carcinoma. This patient was lost to follow-up after 3 weeks; thus, improvement could not be assessed. Another patient with reflux esophagitis had cirrhosis complicated by esophageal varices and discontinued rabeprazole administration after 2 weeks.

The relief rates of subjective symptoms (85.5% and 83.9% for epigastric pain and heartburn combined and heartburn alone, respectively) were comparable to those obtained in previous studies.[19,29]

The 81.6% global improvement rate was lower compared with that found in a previous Phase II study[19] of rabeprazole 10 and 20 mg/d in healthy subjects with lesions but no underlying hepatic disease. The rates of improvement by peptic lesion in this study (100.0%, 88.2%, 80.0%, and 79.4% for stomal, duodenal, and gastric ulcer; and reflux esophagitis, respectively) were lower compared with those found in the Phase II study[19] (100%, 100%, and 96.9% for gastric ulcer treated with rabeprazole 20 mg/d, duodenal ulcer treated with rabeprazole 10 or 20 mg/d, and gastric ulcer treated with rabeprazole 10 mg/d, respectively).[19] These discrepancies might be attributable to the fact that 64.8% of patients enrolled in the present study had cirrhosis, and that factors other than gastric acid secretion might have contributed to the emergence of peptic lesions in patients with preexisting hepatic disease.[18] Some patients discontinued the administration of the drug because of AEs or difficulty receiving the medication orally (in patients with severe hepatic disease) (treatment for ≤2 weeks in ~20% of the patients). These short treatment durations might have contributed to the lower global improvement rate observed in the present study compared with that in the Phase II study.[19]

The global improvement rates stratified by underlying hepatic disorder were 79.0%, 68.8%, and 100.0% for cirrhosis (including hepatocellular carcinoma), chronic hepatitis, and other disorders (alcoholic hepatitis, fatty liver), respectively. Higher rates of improvement were found in hepatic diseases in which hepatic function is retained, including alcoholic hepatitis and fatty liver.

The results of this postmarketing surveillance study suggest that caution should be exercised when treatment with rabeprazole (10 or 20 mg) is initiated in Japanese patients with severe hepatic dysfunction.

CONCLUSION

The results of this study in Japanese patients with hepatic disease suggest that rabeprazole was well tolerated and effective for the treatment of upper GI peptic lesions.

ACKNOWLEDGMENT

This article was sponsored by Eisai Co., Ltd., Tokyo, Japan.

REFERENCES

1. Kamegaya K. Introductory treatises on cirrhosis. In: Kamata T, Mutoh Y, eds. *Integrated Handbook of Internal Medicine 49.* Tokyo, Japan: Nakayama Shoten; 1991:3–52.
2. Ishizaki T. Pharmacokinetics in patients with hepatic disorder. In: Kamata T, Mutoh Y, eds. *Integrated Handbook of Internal Medicine 51.* Tokyo, Japan: Nakayama Shoten; 1992:53–69.
3. Suzuki S, Tei R, Yoshida Y. Cirrhosis. In: Kamata T, Motoh Y, eds. *Integrated Handbook of Internal Medicine 49.* Tokyo, Japan: Nakayama Shoten; 1991:53–69.
4. McCormack TT, Sims J, Eyre-Brook I, et al. Gastric lesions in portal hypertension: Inflammatory gastritis or congestive gastropathy? *Gut.* 1985;26:1226–1232.
5. Papazian A, Braillon A, Dupas JL, et al. Portal hypertensive gastric mucosa: An endoscopic study. *Gut.* 1986;27:1199–1203.
6. D'Amico G, Montalbano L, Traina M, et al, for the Liver Study Group of V. Cervello Hospital. Natural history of congestive gastropathy in cirrhosis. *Gastroenterology.* 1990;99:1558–1564.
7. Ostrow JD, Timmerman RJ, Gray SJ. Gastric secretion in human hepatic cirrhosis. *Gastroenterology.* 1960;38:303–313.
8. Ohto M, Saisho H, Matsutami S, et al. A study on the usefulness of omeprazole (Omepral tablets) in peptic ulcer accompanied by chronic hepatic disorder. *J New Remedies Clin.* 1998;47:39–49.
9. Iwao T, Toyonaga A, Ikegami M, et al. Gastric mucus generation in cirrhotic patients with portal hypertension. Effects of tetraprenylacetone. *Dig Dis Sci.* 1996;41:1727–1732.
10. Garcia Rodriguez LA, Ruigomez A, Jick H. A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom. *Pharmacotherapy.* 1997;17:721–728.
11. Garcia Rodriguez LA, Wallander MA, Stricker BH. The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. *Br J Clin Pharmacol.* 1997;43:183–188.
12. Nishiwaki H, Asai T, Sowa M, Umeyama K. Endoscopic measurement of gastric mucosal blood flow with special reference to the effect of sclerotherapy in patients with liver cirrhosis. *Am J Gastroenterol.* 1990;85:34–37.
13. Toyonaga A, Iwao T, Shimotsuura Y, Tanikawa K. Endoscopic, histologic and haemodynamic studies on portal hypertensive gastric mucosa. *J Gastroenterol Hepatol.* 1989;4(Suppl 1):132–135.
14. Sato N, Kawano S, Nagano K, Tanimura H. Gastric mucosal microcirculatory disturbances in portal hypertension. *J Gastroenterol Hepatol.* 1989;4(Suppl 1):78–80.
15. Solis-Herruzo JA, Pardo-Rueda J. Functional study of the gastric mucosal barrier in hepatic cirrhosis. *Acta Hepatogastroenterol (Stuttg).* 1976;23:351–359.
16. Arakawa T, Satoh H, Fukuda T, et al. Endogenous prostaglandin E2 in gastric mucosa of patients with alcoholic cirrhosis and portal hypertension. *Gastroenterology.* 1987;93:135–140.

17. Mizukami Y, Sakaue H. Gastroduodenal lesions in patients with liver cirrhosis—pathogenesis and management [in Japanese]. *Nippon Rinsho.* 1994;52:91–96.
18. Ichida F, Kihara T. Symposium II. Hepatic diseases and gastrointestinal lesions (excluding esophageal varices). *Gastroenterol Endosc.* 1986;28:1129–1154.
19. Nakazawa S, Namiki M, Matsuo Y, et al. Late phase clinical study of E3810 on gastric and duodenal ulcer-assessment of the optimal dose by a double blind comparative study. *Modern Physician.* 1994;14:38–68.
20. Thjodleifsson B, Rindi G, Fiocca R, et al, for the European Rabeprazole Study Group. A randomized, double-blind trial of the efficacy and safety of 10 or 20 mg rabeprazole compared with 20 mg omeprazole in the maintenance of gastro-oesophageal reflux disease over 5 years. *Aliment Pharmacol Ther.* 2003;17:343–351.
21. Ishizaki T, Horai Y. Review article: Cytochrome P450 and the metabolism of proton pump inhibitors—emphasis on rabeprazole. *Aliment Pharmacol Ther.* 1999;13(Suppl 3): 27–36.
22. Hoyumpa AM, Trevino-Alanis H, Grimes I, Humphries TJ. Rabeprazole: Pharmacokinetics in patients with stable, compensated cirrhosis. *Clin Ther.* 1999;21:691–701.
23. Saigenji K, Yokota K, Kure T, et al. Clinical evaluation of 10 mg tablets in patients with gastric ulcer diseases. *Jpn Pharmacol Ther.* 2002;30:675–693.
24. Good Post-Marketing Surveillance Practice. Japanese Ministry of Health and Welfare Ordinance No. 10. 1997.
25. Sakita T, Miwa T. Endoscopic diagnosis of malignant ulcer. *Jpn J Gastroenterol.* 1970;67:984–989.
26. Armstrong D, Bennett JR, Blum AL, et al. The endoscopic assessment of esophagitis: A progress report on observer agreement. *Gastroenterology.* 1996;111:85–92.
27. Safety Division, Pharmaceutical Affairs Bureau/Ministry of Health and Welfare (PAB/MHW). Criteria for severity grading of ADRs. Tokyo, Japan: PAB/MHW; 1992. Notification no. 80.
28. Pariet (rabeprazole) [package insert]. Tokyo, Japan: Eisai Co., Ltd.; 2003.
29. Yokoyama I, Shibata Y, Kishibe T, et al. Effect of Pariet tablets on early elimination of symptoms in patients with gastric and duodenal ulcers. *Jpn Pharmacol Ther.* 2003;31:93–115.

Address correspondence to: Isao Makino, MD, Megumino Hospital, 2-3-5, Megumino-nishi Eniwa, Hokkaido 061-1395, Japan. E-mail: i-makino@megumino.or.jp