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REVIEW

A Review of the Management of Gastric Acid-Related Diseases

Focus on Rabeprazole

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Motoyasu Kusano, Shikou Kuribayashi, Osamu Kawamura, Yasuyuki Shimoyama, Hiroko Hosaka, Atsuto Nagoshi, Hiroaki Zai and Masatomo Mori

Department of Endoscopy and Endoscopic Surgery, Gunma University Hospital, 3-39-15 Showamachi, Maebashi Gunma 371-8511, Japan. Correponding author email: mkusano@showa.gunma-u.ac.jp

Abstract: Current treatment guidelines for acid-related diseases (ARDs) recommend first-line treatment with a proton pump inhibitor (PPI) to reduce gastric acid production. PPIs are indicated in the management of gastroesophageal reflux disease (reflux esophagitis, nonerosive reflux disease), peptic ulcer (gastric and duodenal ulcer, non-steroidal anti-inflammatory drug (NSAID)-associated ulcer, bleeding ulcer), functional dyspepsia, and in association with *Helicobacter pylori* eradication therapy when needed. Currently, PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are widely used for the treatment of ARDs. All 5 PPIs are effective. However, there are differences in PPI pharmacokinetic and pharmacodynamic profiles that might influence their clinical utility. Rabeprazole is a useful option for the treatment of acid-related diseases due to its rapid onset of acid inhibition and few drug interactions.

Keywords: acid-related diseases, CYP2C19, FSSG, functional dyspepsia, NERD, rabeprazole

Introduction

Proton pump inhibitors (PPIs) are indicated in the management of acid-related diseases (ARDs) and in association with *Helicobacter pylori* (*H. pylori*) eradication therapy when needed. PPIs represent the most important recent advance in the treatment of ARDs. With efficacy profiles superior to those of histamine H2-receptor antagonists (H2RA), and prokinetics, PPIs are now considered the drugs of choice in managing patients with ARDs. Currently, PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are widely used for the treatment of ARDs. All 5 PPIs are effective and safe, however, there are differences in PPI pharmacokinetic and pharmacodynamic profiles that might influence their clinical utility.[1] This article provides an update on the clinical efficacy and safety of rabeprazole when used to treat ARDs.

Onset and Power of Acid Inhibition

The five available PPIs differ in terms of acid stability, depending on various substitutes on the two ring structures. Table 1 shows the pKa of omeprazole, lansoprazole, pantoprazole and rabeprazole, the formation rate of acid-activated compounds at pH 1.2, their pump enzyme inhibitory potency *in vitro*, their acid transport inhibitory potencies in isolated gastric vesicles, and their relative clinical potencies based on 24 h intragastric pH. Rabeprazole has the highest pKa value of these 4 PPIs, and the rapid formation of acid-activated rabeprazole is due to partly its higher pKa.[2] In an *in vitro* acid transport study, rabeprazole achieved maximal inhibition within 8 min of drug exposure, lansoprazole and omeprazole after 20 min

and pantoprazole did not reach a maximum within 30 min.[3] Interestingly, the rate of formation of acid-activated inhibitor correlates with the *in vitro* potencies of PPIs to inhibit gastric pump enzyme activity[4] and acid transport across the vesicle membrane,[5] and also correlates with clinical potency as determined by a comprehensive assessment of dose-dependent effects on intragastric pH.[6]

Differences in pKa also affect accumulation of PPIs. For example, rabeprazole accumulates to 6-fold higher levels than omeprazole (the difference in pKa values is 0.8). The higher accumulation of rabeprazole contributes to faster onset of inhibition of acid secretion, especially in older cells which weakly secrete acid (pH 3).[7] Lysosomes have weakly acidic internal milieu due to the presence of the *V*-type proton pump, which has a completely different molecular structure to the *P*-type gastric pump. Rat kidney lysosome proton pumps were inhibited by a very high concentration of omeprazole *in vitro* (IC_{50} = 75 μM), indicating that lysosomal proton pumps do not have any essential Cys residues that can be blocked by PPIs activated within lysosomes.[8] *In vivo* administration of omeprazole to rats at a dosage 5 times the ED_{50} for gastric acid secretion did not affect the function of liver lysosomes.[9] Higher accumulation of rabeprazole in lysosomes compared with other PPIs may appear to be a demerit, but the lysosomal pumps are not inhibited by the intra-lysosomal presence of rabeprazole or omeprazole. In a comparative trial of 18 *H. pylori* negative adults, rabeprazole 20 mg reached a median 24 h gastric pH of 3.4, as compared with 2.9 for lansoprazole 30 mg, 2.2 for pantoprazole 40 mg, 1.9 for omeprazole 20 mg, and

Table 1. pKa, chemical activation, *in vitro* inhibition of pump activities and clinical efficacy of PPIs.

	Rabeprazole	Omeprazole	Lansoprazole	Pantoprazole	Reference
pKa (pyridine)	4.9	4.1	4.0	4.0	2
The formation rate (t_{50}) of activated compound at pH 1.2 (min)	1.3	2.8	2.0	4.6	3
IC_{50} *in vitro* inhibition of gastric proton pump in isolated vesicles (μM)	0.072	0.47			4
		0.2	0.4	0.6	3
The t_{50} of inhibition of acid transport in isolated vesicles (sec)	90	400	400	1100	5
Relative potencies compared to omeprazole based on 24-h intragastric pH (Caucasian population)	1.82	1.00	0.90	0.23	6

1.3 for placebo (Table 2). Rabeprazole maintained a pH > 4 for 8 h *versus* the other PPIs, which ranged between 3.0 and 7.4 h, $P < 0.04$.[10] Rabeprazole has a rapid onset of action and achieves a maximal or near maximal effect.

Metabolic Pathways

The primary metabolic pathway of rabeprazole is non-enzymatic conversion to rabeprazole-thioether. A minor metabolic pathway is *via* the cytochrome P450 liver isoenzymes CYP2C19 and CYP3A4. Rabeprazole undergoes extensive hepatic metabolism, predominantly nonenzymatic reduction to the thioether and to a lesser extent via CYP2C19 (to desmethyl rabeprazole) and CYP3A4 (to a sulphone metabolite). No metabolites of rabeprazole have any significant antisecretory activity.[11] In comparison with omeprazole, lansoprazole and pantoprazole, the pharmacodynamics of rabeprazole are the least affected by cytochrome P450 (CYP)2C19 genotype (Fig. 1).[12] Multiple-dose studies in healthy volunteers showed no significant effect of CYP2C19 genotype on the effects of rabeprazole on intragastric pH.[13,14] For example, with subjects administered lansoprazole and omeprazole, but not rabeprazole, poor metabolizers had significantly ($P < 0.005$) higher intragastric pH measurements after 7[13] or 8[14] days treatment than homozygous and heterozygous extensive metabolizers. The largely non-enzymatic metabolism of rabeprazole partially accounts for fewer drug–drug interactions between this PPI and other P450 isoenzyme dependent medications. Co-administration of rabeprazole with P450 metabolized medications such as theophylline, diazepam, warfarin and phenytoin does not interfere with their pharmacokinetics.[15] Unlike other PPIs, the hepatic metabolism of rabeprazole is predominantly via nonenzymatic processes and only to a small extent via CYP mediated reactions.[11]

Drug Interactions

Drug interactions mediated by the P450 enzyme family are considered unlikely with rabeprazole.[16] For example, studies have shown no clinically significant interactions between rabeprazole and single oral doses of warfarin or theophylline, nor with single intravenous doses of diazepam or phenytoin.[17] The American Food and Drug Administration has indicated that proton pump inhibitors increase the international normalized ratio (INR) when used concomitantly with warfarin, due to metabolization by cytochrome P450 2C19. We therefore reviewed patients taking warfarin. Two hundred and forty patients administered warfarin after surgery were divided into two groups: Group I (n = 114) administered rabeprazole (10 mg/day) and Group II (n = 126) administered lansoprazole (15 mg/day). The initial dose of warfarin was 3 mg and INR was initially measured on postoperative day 4. The initial INR was significantly lower in Group I (1.66 ± 0.87) than in Group II (2.06 ± 1.03, $P = 0.0011$). Complications of delayed cardiac tamponade and hemothorax were seen in 6 and 1 patients, respectively, in Group II from 5 days to 3 months postoperatively. In contrast, no patients in Group I experienced delayed hemorrhagic complications ($P = 0.015$). Fisher's exact test showed that only lansoprazole was associated with

Table 2. Median pH monitoring values before and on the first day of each proton pump inhibitor treatment. Values in parentheses are 10%–90% confidence intervals.

Pre defined period	RAB	LAN	PAN	OME		PBO
				CAPS	MUPS	
Pre-dose	1.2 (0.8–1.4)	1.3 (0.9–1.9)	1.2 (0.9–2.0)	1.3 (1.0–2.0)	1.2 (1.0–2.2)	1.1 (0.8–1.8)
Post-dose	3.4 (1.9–4.2)*†‡§¶	2.9 (1.8–3.9)†‡§¶	2.2 (1.4–4.2)¶	1.9 (1.2–3.2)¶	1.8 (1.3–4.5)¶	1.3 (1.1–1.9)
Daytime	3.6 (2.3–4.2)†§¶	3.3 (2.1–4.3)†‡§¶	2.2 (1.3–3.7)¶	1.8 (1.2–4.2)¶	2.1 (1.2–4.2)¶	1.3 (1.0–2.0)
Night-time	2.3 (1.3–5.7)†§¶	2.1 (1.5–4.1)¶	1.6 (1.0–4.4)¶	1.6 (1.2–4.5)	1.5 (1.2–6.8)	1.2 (0.9–2.2)

Notes: *$P < 0.03$ vs. LAN (Wilcoxon signed rank test for paired data); †$P < 0.03$ vs. PAN (Wilcoxon signed rank test for paired data); ‡$P < 0.02$ vs. OME CAPS (Wilcoxon signed rank test for paired data); §$P < 0.04$ vs. OME MUPS (Wilcoxon signed rank test for paired data); ¶$P < 0.04$ vs. PBO (Wilcoxon signed rank test for paired data).
Abbreviations: CAPS, capsule; LAN, lansoprazole; MUPS, multiple unit pellet system; OME, omeprazole; PAN, pantoprazole; PBO, placebo; RAB, rabeprazole. Pre-dose period, 08.00–08.30 h; Post-dose period, 08.30–08.00 h; Daytime period, 08.30–22.30 h; Night-time period, 22.30–06.30 h.
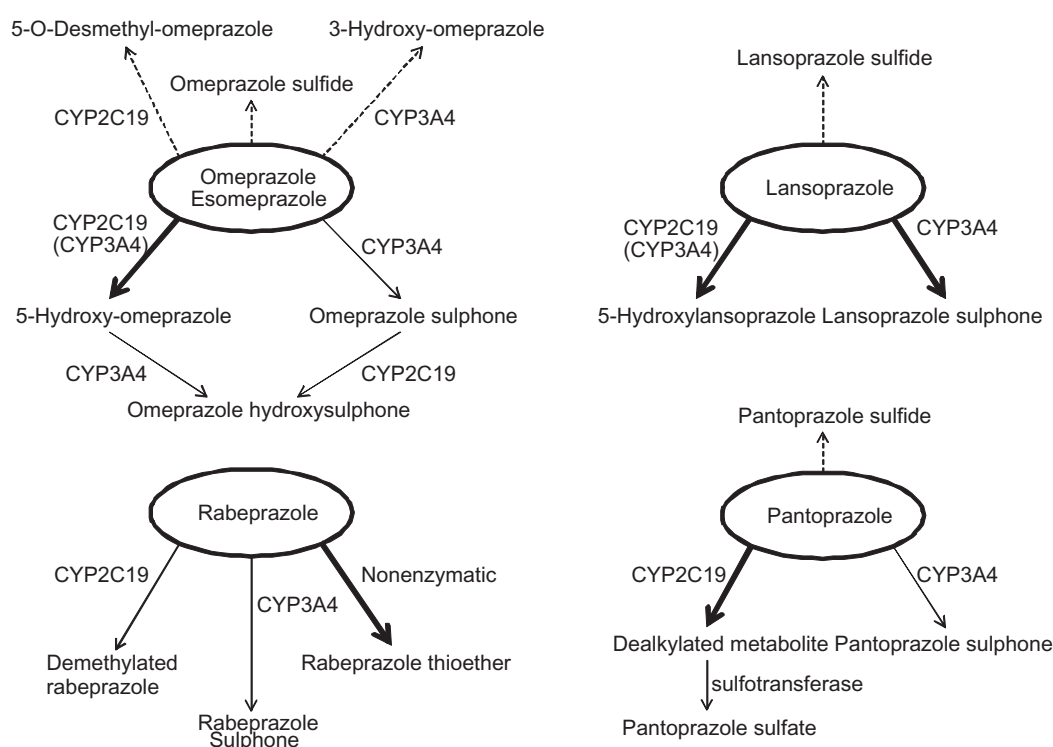
Figure 1. Metabolic pathways for omeprazole and esomeprazole, lansoprazole, rabeprazole and pantoprazole. The thickness of the arrows indicates the approximate contribution of each cytochrome P450 (CYP) isoform to each of the metabolic pathways.
Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors-emphasis on rabeprazole. *Aliment Pharmacol Ther.* 1999 Aug;13 Suppl 3:27–36; Horai Y, Kimura M, Furuie H, et al. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. *Aliment Pharmacol Ther.* 2001 Jun;15(6):793–803.

bleeding events ($P = 0.0151$). These results suggest that lansoprazole enhances the effects of warfarin. Rabeprazole can be safely used concomitantly with warfarin.[18] Recent evidence has shown that clopidogrel and PPIs are metabolized by the same pathway, and that patients taking both drugs have greater levels of platelet reactivity and more adverse outcomes than patients taking only clopidogrel.[19] Clopidogrel is a pro-drug that is metabolized to its active ingredient by hepatic cytochrome P-450 isoenzymes, with isoenzyme CYP2C19 playing a major role.[20] PPIs may also competitively inhibit CYP2C19 metabolism. *In vitro* testing of a model substrate showed that lansoprazole and omeprazole were the most potent inhibitors, whereas pantoprazole and rabeprazole were the least potent, with inhibition constants (Ki) for the latter PPIs above their pharmacologically relevant concentrations generally achieved *in vivo*.[21] Patients taking aspirin 100 mg plus clopidogrel 75 mg/day were assigned to groups administered rabeprazole 10–20 mg/day or without rabeprazole, prospectively. The decision to administer RPZ or not was at the discretion

of the treating physician. The pharmacodynamic endpoint, platelet aggregation, and the clinical endpoint, cardiovascular adverse events, were followed up at 1 year. Platelet aggregation was higher with than without rabeprazole, although the difference was not statistically significant. No differences were seen in cardiovascular adverse events between groups. No significant interaction was detected between rabeprazole and clopidogrel.[22] When concomitant use of a PPI and clopidogrel is considered, rabeprazole may be safer than other PPIs.

Clinical Efficacy in the Treatment of ARDs

Gastroesophageal reflux disease (GERD)

GERD is a common condition with an increasing prevalence in Western nations. In Japan, the prevalence of GERD has been on the increase since the end of the 1990s. The reasons for the increase in the reported prevalence of GERD may involve increased gastric acid secretion, a decrease in the *H. pylori* infection rate, increased awareness of GERD, and advances in

the concept of GERD.[23] Furthermore, although many GERD patients may present with typical symptoms such as heartburn and acid regurgitation, others may complain mainly of atypical symptoms such as epigastric pain or pressure, nausea/vomiting, hoarseness, chest pain, or wheeze.[24] Symptom assessment, management and resolution remain the primary goals of medical intervention for both patients and physicians. Evaluation of the response of GERD symptoms to treatment, however, has been hampered by the lack of a valid, reliable, highly responsive, and easy to use assessment tool.[25]

We conducted a survey of the actual symptoms of Japanese GERD patients. A total of 124 patients with an endoscopic diagnosis of GERD completed a 50 part questionnaire (requiring only 'yes' or 'no' answers) that covered various symptoms related to the upper gastrointestinal tract, including psychosomatic symptoms. We extracted the 12 questions to which patients most often answered 'yes' and produced a multiple choice questionnaire that graded the frequency of each symptom (never = 0, occasionally = 1, sometimes = 2, often = 3, and always = 4), that we named

the Frequency Scale for Symptoms of GERD (FSSG, Fig. 2). A significant reduction in the FSSG score occurs in patients with both mild and severe GERD after PPI therapy.[26] The FSSG contains the 12 symptoms most commonly experienced by GERD patients, with 7 of the 12 related to reflux symptoms and the remaining 5 to dyspeptic symptoms. Sixty-eight GERD patients receiving proton pump inhibitor therapy completed the questionnaire before and after treatment for 8 weeks. A significant positive correlation was seen between reflux symptoms and acid-related dyspepsia before and after therapy (r = 0.569 and r = 0.569; both P's < 0.001), and acid-related dyspepsia in patients with both NERD and RE. We concluded that GERD patients suffer not only from reflux symptoms, but also from acid-related dyspepsia, and PPIs improve both types of symptoms.[27] The clinical efficacy of rabeprazole in the management of GERD has been evaluated in terms of symptom relief,[28–33] healing[34–37] and maintenance therapy[34–37] of reflux esophagitis (RE), and in the symptomatic relief of non-erosive reflux disease (NERD)[38–40] or uninvestigated GERD.[41,42]

F-scale — **F.S.S.G. (Frequency Scale for the Symptoms of GERD)** DATE:

* Do you have any of following symptoms? If so, please circle the appropriate response below.

NAME (ID;) AGE GENDER M · F

Question	Fill-in space				
	NEVER	OCCA-SIONALLY	SOME-TIMES	OFTEN	ALWAYS
1 Do you get heartburn?	0	1	2	3	4
2 Does your stomach get bloated?	0	1	2	3	4
3 Does your stomach ever feel heavy after meals?	0	1	2	3	4
4 Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
5 Do you ever feel sick after meals?	0	1	2	3	4
6 Do you get heartburn after meals?	0	1	2	3	4
7 Do you have an unusual (e.g. burning) sensation in your throat?	0	1	2	3	4
8 Do you feel full while eating meals?	0	1	2	3	4
9 Do some things get stuck when you swallow?	0	1	2	3	4
10 Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
11 Do you burp a lot?	0	1	2	3	4
12 Do you get heartburn if you bend over?	0	1	2	3	4

Please describe any other symptoms you experience.

SUM POINTS □ + □ + □ + □ = □

Acid reflux related symptom = □ POINTS
Dyspeptic (Dysmotility) symptom = □ POINTS

Figure 2. The FSSG (Frequency Scale for the Symptoms of GERD) asks questions about the 12 symptoms most commonly experienced by GERD patients, with 7 of the 12 related to reflux symptoms and the remaining 5 to dyspeptic symptoms.
Kusano M, et al. *J Gastroenterol*. 2004 Sep;39(9):888–91; Kusano M, et al. *Dig Dis Sci*. 2007 Jul;52(7):1673–7.
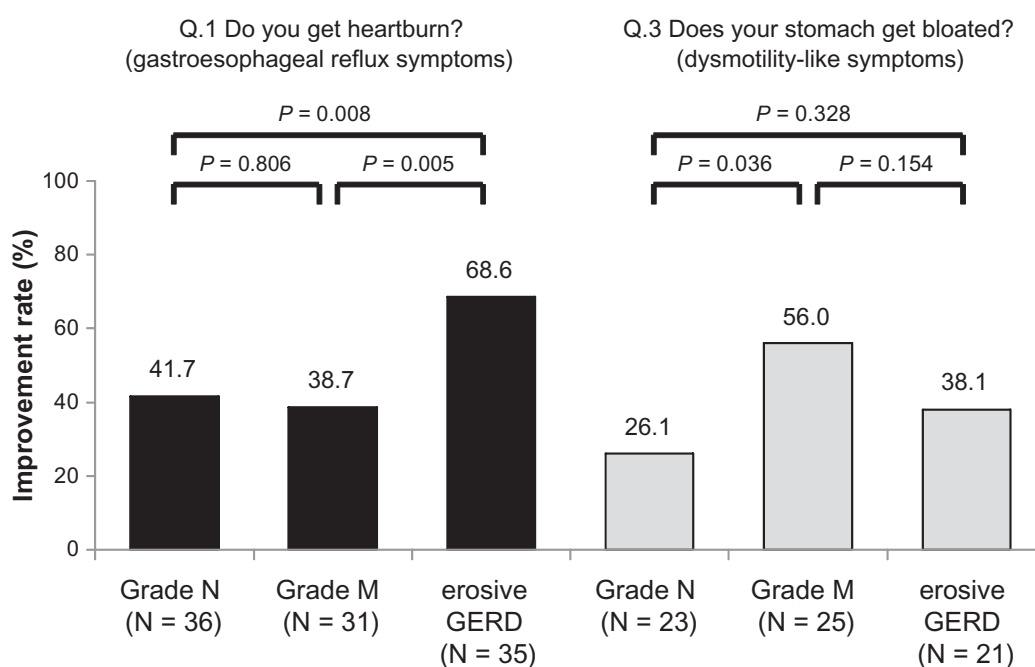
Figure 3. Questions with significant differences in improvement rates between groups for gastroesophageal reflux symptoms (Q1 Black bars) and dysmotility-like symptoms (Q3 Gray bars).
Note: This analysis was conducted only for questions the authors considered clinically meaningful, where the ratio of analysis subjects answering 'yes' before treatment (i.e. symptomatic) was >30% in every group.

Reflux esophagitis (RE)

Participants in studies evaluating rabeprazole for the acute treatment of erosive or ulcerative GERD[28–33,43] were required to be symptomatic, with endoscopically confirmed lesions at (or prior to) study entry. Patients were administered rabeprazole 10 or 20 mg once daily or a comparator PPI or placebo for 1[28] or 4[29–33,43] weeks, with endoscopic assessment performed at baseline and after 4[29,30,32] and/or 8[29,43] weeks of study treatment in all[23–27,37] but the week-long trial.[22] Rabeprazole was effective in the acute symptomatic treatment and healing of erosive or ulcerative GERD in well-designed trials of 1[28] or 4–8[39–34] weeks' duration. Studies of RE have aimed to identify differences in the speed of symptom relief and mucosal healing. In one study, RE patients were randomized to receive omeprazole 20 mg/day, lansoprazole 30 mg/day or rabeprazole 20 mg/day for 8 weeks.[39] Symptoms were assessed daily for the first 7 days of administration. Whereas there was a decrease in the mean heartburn score with rabeprazole therapy at the initial study interval of 1 week, the 8 week comparison showed no difference in the endoscopic rate of RE healing. Although pharmacokinetic differences are seen with CYP2C19 polymorphism, the CYP2C19 genotype did not affect healing rates at 4 and 8 weeks in 103 Japanese patients

with erosive GERD. Oesophageal healing rates in patients identified as homozygous-extensive metabolizers, heterozygous-extensive metabolizers and poor metabolizers after 4 weeks' treatment with rabeprazole 10 mg were 86.1%, 92.0% and 82.4%, respectively. The corresponding healing rates at 8 weeks were 86.1%, 92.0% and 82.4%, showing no significant differences between genotypes in terms of healing rate at either time point.[43] The study endpoints included time to endoscopically confirmed GERD relapse[37] and frequency of heartburn relapse.[34,36] Patient discontinuations during the 5 years were more common in the placebo group than in the rabeprazole groups. Clinical relapse was the primary reason for early treatment termination in 59% of the placebo group, compared with 15% and 7% of the rabeprazole 10 and 20 mg/day groups, respectively. The median time to relapse was 1848 days in the rabeprazole 10 mg/day group (no relapse in the 20 mg/day group) compared with 32 days with placebo ($P = 0.0001$ for both rabeprazole dosages vs. placebo; $P = 0.007$ for rabeprazole 20 vs. 10 mg/day). Relapse rates for heartburn frequency were also significantly lower in the rabeprazole than placebo groups.[34,36] Heartburn frequency relapse rates differed significantly between rabeprazole and placebo groups at all timepoints during the

5 year study. From weeks 4 to 260, the heartburn frequency relapse rates were 21%–39% in the rabeprazole 20 mg group, 22%–48% in the rabeprazole 10 mg group, and 68%–78% in the placebo group.[36]

Non-erosive reflux disease (NERD)

Symptom relief with 4 weeks of rabeprazole treatment in patients with NERD was rapid.[44] We combined data from two similarly designed, double-blind, placebo-controlled, multicenter US trials in which 261 patients were asked to record daily their acid reflux symptoms. The median time to 24 h heartburn-free status was significantly shorter in the rabeprazole group (3.5 versus 19 days in the placebo group), and complete heartburn relief at 4 weeks was 32% in the rabeprazole group vs. 3.8% in the placebo group ($P < 0.0002$). The median time to the first 24 h interval without heartburn symptoms was significantly shorter in the rabeprazole 10 and 20 mg/day groups (2.5 and 4.5 days) than in the placebo group (21.5 days; $P = 0.004$) in a 4 week, placebo-controlled trial with patients with NERD. Approximately 30% of patients administered rabeprazole reported complete heartburn relief at week 4 (compared with 3.4% of those administered placebo), and both rabeprazole dosages significantly reduced daytime and nighttime heartburn scores over the first 2 days of treatment ($P < 0.01$).[40] Symptoms of regurgitation, belching, bloating, nausea and early satiety were also significantly ameliorated with rabeprazole treatment ($P < 0.01$).[40] Rabeprazole was effective as on-demand, long-term maintenance therapy in patients with NERD or uninvestigated GERD, and was an acceptable alternative to continuous once-daily rabeprazole in patients with NERD.[28,42]

In another study, Japanese patients with NERD were classified as grade N (endoscopically normal), M (minimal change), or erosive GERD, and answered a 51 item, yes or no questionnaire pre and post-treatment. Compared to erosive GERD, clear differences existed in pretreatment prevalence of symptoms and responsiveness to 4 weeks of rabeprazole 10 mg/day in grades N and M. These results suggest that stomachaches (especially at night) were significant symptoms in patients with grade N disease, and dysmotility-like symptoms such as abdominal bloating were significant in those with grade M disease, whereas gastroesophageal reflux symptoms were significant in those with erosive GERD. The clinical significance

of classifying NERD was indicated from the different symptoms and responsiveness to rabeprazole.[38] Rabeprazole provides early symptom control in patients with NERD, and is therefore appropriate for both continuous and on-demand therapy, as demonstrated in clinical trials. Further trials evaluating on-demand PPI therapy, including rabeprazole, are needed in patients with erosive GERD.[45]

Supraesophageal manifestations of gastroesophageal reflux disease

Supraesophageal manifestations of GERD include asthma, cough, laryngopharyngeal reflux (LPR), non-cardiac chest pain (NCCP) and sleep disorders.

Asthma, cough

Sugawa et al established a novel rat model and examined the pathogenic interaction between RE and bronchial asthma. RE and bronchial asthma were induced in Brown-Norway rats by ligating the transitional region between the forestomach and glandular stomach and wrapping the duodenum near the pylorus, and by ovalbumin sensitization and challenge with ovalbumin aerosol. Significant increases in the number of cells, especially eosinophils, and IL-13 but not IFN-gamma concentration, were observed in bronchoalveolar lavage fluid (BALF) in the RE + bronchial asthma group compared with the bronchial asthma group. These augmentations of ovalbumin-induced airway inflammation were prevented by treatment with rabeprazole.[46] Improvement in peak expiratory flow (PEF: a measure of the severity of obstructive airways disease) has been demonstrated in patients suffering from concomitant asthma and GERD. Treatment with rabeprazole 20 mg/day was found to improve PEF by >20% in 40% of non-steroid dependent asthma patients.[47]

Laryngopharyngeal reflux (LPR)

LPR has also been reported to be a major cause of laryngeal inflammation, and presents with a constellation of symptoms that differ from those of GERD.[48] Koufman was the first to clearly distinguish LPR from GERD, noting that patients with LPR rarely complain of typical GERD symptoms, such as heartburn and acid reflux.[49] Acid-suppression therapy with a PPI is considered the mainstay of treatment for LPR. In a study with 100 patients with LPR symptoms, upper

abdominal and LPR symptoms were evaluated using both the FSSG and the LPR symptom scoring system. In the 52 subjects with LPR, changes in these symptoms with rabeprazole 20 mg/day for at least 4 weeks were evaluated. There were significant reductions in the frequency of acid reflux-related symptoms, dysmotility-like symptoms, and laryngopharyngeal symptoms after rabeprazole therapy. The LPR symptom score decreased to less than half the pretreatment score in 25 subjects (therapeutic response group). The pretreatment frequency of dysmotility-like symptoms appeared higher in the nonresponse group than in the response group, although the difference was not significant. No significant difference was seen between the two groups in the pretreatment frequency of acid reflux-related symptoms. The frequency of dysmotility-like symptoms was similar to that of acid reflux-related symptoms. The pretreatment frequency of dysmotility -like symptoms, but not that of acid reflux-related symptoms, might be a predictor of patient response to rabeprazole.[50]

Non-cardiac chest pain (NCCP)

The use of rabeprazole in the empirical diagnosis of GERD-related chest-pain (the so called PPI test) was assessed in a recent double-blind, randomized, placebo-controlled, crossover trial, that demonstrated a sensitivity of 75% and a specificity of 90% for rabeprazole 20 mg bid, administered for 7 days as a therapeutic trial.[51] Kim et al compared the efficacy of one-week and two-week PPI trial in patients with NCCP at least weekly, with the aim of determining the optimal duration for the diagnosis of GERD-related NCCP. There was no significant difference in the rate of positive PPI tests between the GERD-related NCCP group and the non GERD-related NCCP group during the first week of the PPI test. However, during the second week, the GERD-related NCCP group had a higher positive PPI test rate (n = 13, 81%) than the non GERD-related NCCP group (n = 7, 27%) ($P = 0.001$) with a sensitivity and specificity of 81% and 62%, respectively. The rabeprazole empirical trial was diagnostic for patients with GERD-related NCCP, with an optimal duration of at least two weeks.[52]

Sleep disorders

Sleep dysfunction, defined as a PSQI score > 5.5, was detected in 70 (52.2%) of patients with GERD.

NERD was significantly associated with sleep dysfunction compared to erosive reflux disease (OR 2.18, 95% CI: 1.05–4.53). Rabeprazole 10 mg/day for 8 weeks led to an effective decrease in sleep dysfunction. Acid plays an important role in sleep dysfunction in all patients with GERD.[53]

Peptic ulcer

NSAID use and *H. pylori* infection are both well recognized as contributors to the aetiology of peptic ulcer disease.

Gastric and duodenal ulcer

The efficacy of rabeprazole in the treatment of peptic ulcer has been evaluated in three randomized, double-blind, multicenter comparisons with omeprazole.[54–56] In two trials comparing rabeprazole 20 mg/day with omeprazole 20 mg/day, there were no significant differences between rabeprazole and omeprazole in terms of symptom resolution based on most of the 12 symptom-related efficacy indices.[55,56] However, in one of the studies, significant differences were seen between treatment groups in terms of the proportion of patients with improvement (defined as any decrease from baseline) in gastric ulcer pain frequency after 6 weeks' treatment (82% for rabeprazole vs. 65% for omeprazole; $P = 0.006$), day pain severity after 3 weeks (88% vs. 75%; $P = 0.023$) and resolution of night pain after 6 weeks (84% vs. 68%; $P = 0.022$).[54]

Ando et al[57] demonstrated that the healing efficacy of rabeprazole is less influenced by CYP2C19 genetic polymorphism than that of omeprazole and that this advantage can result in earlier repair of gastric mucosal damage. Eighty patients with active gastric ulcer were administered rabeprazole 10 mg or omeprazole 20 mg once daily for 8 weeks. Reuction in gastric ulcer size and ulcer healing rates were stratified according to CYP2C19 metabolizer subgroup after 2 and 8 weeks of treatment. Percentage ulcer area healing ratios were more consistent across subgroups in the rabeprazole group at 2 weeks (80.7 ± 17.4% vs. 89.3 ± 12.5% vs. 84.3 ± 13.2%, respectively, for homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers), than in the omeprazole group (63.4 ± 24.6% vs. 85.2 ± 12.2% vs. 84.0 ± 16.4%, $P = 0.0347$ rabeprazole vs. omeprazole in homozygous extensive metabolizers),

resulting in an overall significant difference (85.9 ± 14.4% vs. 76.5 ± 21.0%, $P = 0.0210$ rabeprazole vs. omeprazole total healing rate).

Non-steroidal anti-inflammatory drug (NSAID) ulcer

An alternative strategy is to protect the GI mucosa from damage through acid suppression. It is known that maintaining an intragastric pH > 4 heals gastric ulcers, and that in patients taking NSAIDs, the extent of NSAID-associated gastric damage is pH dependent.[58] The level of acid suppression provided by H2RAs at traditional dosages does not prevent most NSAID-related gastric ulcers. Sugimoto et al investigated whether aspirin induces esophageal mucosal injury, and whether rabeprazole can prevent such injury in relation to CYP2C19 genotypes. Fifteen healthy Japanese volunteers underwent a 7 day randomized 5-way crossover trial: placebo, aspirin 100 mg, rabeprazole 10 mg, and aspirin 100 mg plus rabeprazole 10 mg either once daily or 4 times per day. All subjects underwent endoscopy and 24 h intragastric pH monitoring on day 7. With the aspirin regimen, esophageal mucosal damage was seen in 7 subjects (46.7%). The median pH in grade A GERD was significantly lower (1.5) than in patients without GERD (5.6, $P = 0.04$). Rabeprazole significantly inhibits acid secretion irrespective of CYP2C19 genotype, and decreases the incidence of aspirin-related esophageal injury and symptoms according to the increase in pH.[59]

Nishino et al investigated whether aspirin-induced gastric mucosal injury might have any association with the intragastric pH. Fifteen healthy, *H. pylori*-negative volunteers randomly underwent the four different 7-day regimens: (1) aspirin 100 mg, (2) rabeprazole 10 mg, (3) aspirin 100 mg + rabeprazole 10 mg, and (4) aspirin 100 mg + rabeprazole 40 mg. Gastric mucosal injury was evaluated using the modified Lanza score (MLS), 24 h intragastric pH monitoring, and histopathology of the gastric mucosa, prior to commencement and on day 7 of each regimen. The median MLS was 0 at baseline and for the rabeprazole 10 mg regimen. The median MLS in the aspirin regimen was 3, and 0 for both the aspirin + rabeprazole 10 mg and aspirin + rabeprazole 40 mg regimens. Rabeprazole significantly prevented aspirin-induced gastric mucosal injury ($P = 0.001$ for rabeprazole 10 mg and $P = 0.005$ for rabeprazole 40 mg).

The MLS negatively correlated with 24 h intragastric pH ($r = -0.711$, $P < 0.001$), whereas aspirin had no effect on intragastric pH. Aspirin increased the mean gastric mucosa microvessel diameter, which in turn correlated negatively with intragastric pH.[60] In Japan, Mizokami investigated the efficacy and safety of rabeprazole coadministered with continuous non-steroidal anti-inflammatory drug (NSAID) in treating NSAID-induced ulcer. Upper gastrointestinal endoscopy of patients on continuous NSAID treatment revealed an ulcerous lesion (open ulcer) with diameter ≥3 mm. Endoscopies were performed at the start of treatment, during the treatment period, and at the conclusion (or discontinuation) of treatment. Findings were evaluated in terms of size (maximum diameter) and stage based on the Sakita-Miwa classification. An ulcer was regarded as cured when the 'white coating' was seen to have disappeared at endoscopy. In the safety evaluation, all medically untoward symptoms and signs (adverse events, laboratory abnormalities, incidental symptoms, etc.) occurring after the commencement of rabeprazole treatment were considered adverse events. The endoscopic cure rate in 38 patients in the efficacy analysis group (endoscopic evaluation) was 71.1% (27/38). Of those 38 patients, 35 had a gastric ulcer, with a cure rate of 71.4% (25/35), and 3 a duodenal ulcer, with a cure rate of 66.7% (2/3). The treatment efficacy of rabeprazole for NSAID-induced ulcer under continuous NSAID administration was confirmed.[61]

Bleeding ulcer

Clinicians have debated for many years concerning the role of antisecretory therapy in the management of gastrointestinal (GI) bleeding from peptic ulcers. The theoretical basis for use of these agents is that (1) gastric acid and pepsin inhibit clot formation and cause clot lysis, and (2) gastric acid impairs ulcer healing. Unfortunately, early studies assessing the efficacy of H2RAs in the management of GI bleeding were disappointing. Many researchers hypothesized that the high failure rate was related to the inability of H2RAs to provide gastric pH values above 6, the level required to achieve hemostasis.[62–64] Uedo et al conducted a prospective randomized controlled trial at a tertiary cancer center, investigating whether PPIs more effectively prevents bleeding than H2RAs following the recently developed technique of endoscopic submucosal dissection (ESD) for early

gastric cancer (EGC). A total of 143 patients with EGC who underwent ESD were randomly assigned on the day before ESD to treatment with either rabeprazole 20 mg (PPI group) or cimetidine 800 mg (H2RA group), which was continued for 8 weeks. The primary end point was the incidence of bleeding, defined as hematemesis or melena that decreased the patient's hemoglobin by more than 2 g/dL and required endoscopic hemostasis. Bleeding occurred in 6.1% (4/66) of patients in the PPI group and 17.2% (11/64) of the H2RA group ($P = 0.057$). Multivariate analysis revealed that PPI treatment significantly reduced the risk of bleeding (adjusted hazard ratio 0.47, 95% confidence intervals 0.22–0.92, $P = 0.028$). Rabeprazole prevented delayed bleeding from the ulcer created at ESD more effectively than did cimetidine.[65]

Zollinger Ellison syndrome

The key to successfully reducing acid output in patients with Zollinger Ellison syndrome (ZES) is to adjust the PPI dosage regimen to meet the individual patient's needs. The dosage of rabeprazole in patients with a pathological hypersecretory condition varies with the individual patient. The recommended adult oral starting dosage for ZES is 60 mg once daily. The dosage should be adjusted to the individual patient's needs, and treatment should continue for as long as clinically indicated.[66]

Helicobacter pylori eradication

The benefits of *H. pylori* eradication in patients with peptic ulcer include more rapid ulcer healing, reduced ulcer recurrence, and a reduction in hemorrhagic complications.[67] Combination therapies with a PPI plus two or three antibacterial agents are well established for this purpose, with the most widely used antibacterial combination being clarithromycin and amoxicillin. Rabeprazole has demonstrated good *in vitro* antibacterial activity against *H. pylori*. In an *in vitro* study using 133 strains of *H. pylori* isolated from patients with gastric and/or duodenal ulcer, the minimum inhibitory concentration at which 90% of the tested isolates were inhibited (MIC90) was 0.5 mg/mL for rabeprazole and 0.25 mg/mL for the rabeprazole thioether metabolite, whereas the MIC90 values for lansoprazole and omeprazole were 1 mg/mL and 16 mg/mL, respectively.[68] In general, shorter courses (7 days vs. 10–14 days) of *H. pylori*

eradication triple therapy are common in Europe. In the US, lansoprazole and esomeprazole are currently indicated for *H. pylori* eradication, having demonstrated high eradication rates in combination with amoxicillin + clarithromycin over 10–14 days and 10 days, respectively. However, rabeprazole has recently been approved by the US FDA for *H. pylori* eradication as part of a 7 day regimen, also in combination with amoxicillin + clarithromycin. *H. pylori* eradication rates with rabeprazole plus clarithromycin + amoxicillin triple therapy do not differ significantly from those observed with triple therapy with omeprazole,[69,70] esomeprazole[69,71] or pantoprazole,[69] but are greater than with lansoprazole[72] containing regimens. The reported eradication rates in the rabeprazole + amoxicillin + clarithromycin (RAC) regimen were 88% (130/147) based on intention-to-treat analysis conducted in all subjects, and 91% (130/143) based on per protocol analysis conducted after excluding dropouts. For the lansoprazole + amoxicillin + clarithromycin (LAC) regimen, the eradication rates were 78% (116/148) according to intention-to-treat analysis and 81% (116/144) according to per protocol analysis. Both intention-to-treat ($P < 0.05$) and per protocol analyses ($P < 0.01$) showed significantly higher eradication rates for RAC than LAC.[72] It has been suggested that the greater direct antibacterial activity of rabeprazole, its fast onset of action and its predominantly nonenzymatic route of metabolism, and consistent acid inhibition across CYP2C19 genotypes, may result in increased antimicrobial efficacy allowing shorter triple therapy regimens. This warrants further investigation.[73]

Functional dyspepsia (FD)

The consensus guidelines recommend PPIs for the treatment of FD.[74] Empiric PPI treatment would be expected to provide symptom relief to the majority of dyspepsia sufferers who present in clinical practice. PPIs represent the best currently available therapy for ARDs and should be considered the first-line management approach in patients with uninvestigated dyspepsia.[75] In healthy volunteers, rabeprazole 20 mg bid did not significantly alter gastric emptying, but reduced symptoms and had a borderline effect on postprandial gastric volume. The mechanism of reduction of postprandial symptoms by rabeprazole requires further study.[76] In another study, 97 Japanese

patients diagnosed with FD according to the Rome III criteria were randomized to either rabeprazole 10 mg once daily (N = 46) or itopride 50 mg tid (N = 51) for 4 weeks. As reported in Western patients, faster onset of action was seen with rabeprazole compared to itopride in Japanese FD patients. For epigastric pain syndrome (EPS), rabeprazole showed faster onset and greater improvement than Itopride. However, for postprandial distress syndrome (PDS), itopride showed faster onset of action but not significantly more symptomatic improvement, than rabeprazole.[77,78] Tominaga et al conducted the CAESAR study (Clinical Assessment to Establish the Symptomatic Advantage of Rabeprazole: a double-blind randomized placebo-controlled study) to examine the efficacy of rabeprazole in improving the symptoms of FD. They randomly assigned 98 subjects with FD, diagnosed according to the Rome III criteria, to 4 weeks of either rabeprazole 10 mg/day or placebo. The severity of gastrointestinal symptoms was assessed using the Gastrointestinal Symptoms Rating Scale (GSRS) at baseline and at weekly intervals during the treatment period. The primary endpoint was change in scores for each item of the GSRS following treatment. Four weeks' treatment with rabeprazole decreased reflux domain scores (2.5 ± 0.2 to 1.5 ± 0.1) compared to placebo (2.5 ± 0.2 to 1.9 ± 0.1, $P = 0.0232$). Significant differences were seen in the changes from baseline in the regurgitation and nausea scores between rabeprazole and placebo. Rabeprazole is clinically beneficial in ameliorating FD symptoms in Japanese patients, in particular for overlapping regurgitation and nausea symptoms.[79]

Summary and Conclusion

The physicochemical and pharmacokinetic profiles of PPIs can influence their safety and efficacy in clinical practice. Rapid symptom relief is a key feature of therapy for patients with ARDs. Rabeprazole is a useful option for the treatment of ARDs, and provides a valid alternative to the other currently available PPIs, with the added benefits of having a favorable efficacy profile and low incidence of drug interactions.

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Disclosures

References

1. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practicing physician needs to know. *Drugs*. 2003;63(24):2739–54.
2. Huber R, Kohl B, Sachs G, Senn-Bilfinger J, Simon WA, Sturm E. Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. *Aliment Pharmacol Ther*. 1995 Aug;9(4):363–78.
3. Kromer W, Krüger U, Huber R, et al. Differences in pH-dependent activation rates of substituted benzimidazoles and biological in vitro correlates. *Pharmacology*. 1998 Feb;56(2):57–70.
4. Morii M, Takata H, Fujisaki H, et al. The potency of substituted benzimidazoles such as E3810, omeprazole, Ro 18-5364 to inhibit gastric H+, K+-ATPase is correlated with the rate of acid-activation of the inhibitor. *Biochem Pharmacol*. 1990 Feb 15;39(4):661–7.
5. Besancon M, Simon A, Sachs G, et al. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. *J Biol Chem*. 1997 Sep 5;272(36):22438–46.
6. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. *Eur J Clin Pharmacol*. 2009 Jan;65(1):19–31.
7. Sachs G. Improving on PPI-based therapy of GORD. *Eur J Gastroenterol Hepatol*. 2001 May;13 Suppl 1:S35–41.
8. Simon WA, Keeling DJ, Laing SM, et al. Biochemistry of a novel (H+ + K+)-ATPase inhibitor. *Biochem Pharmacol*. 1990 Jun 1;39(11):1799–806.
9. Grinpukel S, Sewell R, Yeomans N, et al. Lack of effect of omeprazole, a potent inhibitor of gastric (H+ + K+) ATPase, on hepatic lysosomal integrity and enzyme activity. *J Pharm Pharmacol*. 1986 Feb;38(2):158–60.
10. Pantoflickova D, Dorta G, Ravic M, et al. Acid inhibition on the first day of dosing: comparison of four proton pump inhibitors. *Aliment Pharmacol Ther*. 2003 Jun 15;17(12):1507–14.
11. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors-emphasis on rabeprazole. *Aliment Pharmacol Ther*. 1999 Aug;13 Suppl 3:27–36.
12. Horai Y, Kimura M, Furuie H, et al. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. *Aliment Pharmacol Ther*. 2001 Jun;15(6):793–803.
13. Adachi K, Katsube T, Kawamura A, et al. CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. *Aliment Pharmacol Ther*. 2000 Oct;14(10):1259–66.
14. Shirai N, Furuta T, Moriyama Y, et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. *Aliment Pharmacol Ther*. 2001 Dec;15(12):1929–37.
15. Thjodleifsson B, Cockburn I. Review article: rabeprazole's tolerability profile in clinical trials. *Aliment Pharmacol Ther*. 1999 Oct;13 Suppl 5:17–23.
16. Blume H, Donath F, Warnke A, et al. Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Saf*. 2006;29(9):769–84.
17. Humphries TJ, Merritt GJ. Review article: drug interactions with agents used to treat acid-related diseases. *Aliment Pharmacol Ther*. 1999 Aug;13 Suppl 3:18–26.
18. Hata M, Hayasaka M, Sezai A, et al. Proton pump inhibitors may increase the risk of delayed bleeding complications after open heart surgery if used concomitantly with warfarin. *Thorac Cardiovasc Surg*. 2008 Aug;56(5):274–7.

19. Gaglia MA Jr, Torguson R, Hanna N, et al. Relation of proton pump inhibitor use after percutaneous coronary intervention with drug-eluting stents to outcomes. *Am J Cardiol*. 2010 Mar 15;105(6):833–8.

20. Savi P, Pereillo JM, Uzabiaga MF, et al. Identification and biological activity of the active metabolite of clopidogrel. *Thromb Haemost*. 2000 Nov; 84(5):891–6.

21. Li XQ, Andersson TB, Ahlstrhl M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos*. 2004 Aug;32(8):821–7.

22. Hokimoto S, Ogawa H, Yamamoto K, et al. Is impact of proton pump inhibitor on platelet reactivity to clopidogrel a class effect? *Circulation*. 2009;120: S1033. Abstract 5010.

23. Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. *J Gastroenterol*. 2009;44(6):518–34.

24. Wong WM, Fass R. Extraesophageal and atypical manifestations of GERD. *J Gastroenterol Hepatol*. 2004 Sep;19 Suppl 3:S33–43.

25. Fass R. Symptom assessment tools for gastroesophageal reflux disease (GERD) treatment. *J Clin Gastroenterol*. 2007 May–Jun;41(5):437–44.

26. Kusano M, Shimoyama Y, Sugimoto S, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol*. 2004 Sep; 39(9):888–91.

27. Kusano M, Shimoyama Y, Kawamura O, et al. Proton pump inhibitors improve acid-related dyspepsia in gastroesophageal reflux disease patients. *Dig Dis Sci*. 2007 Jul;52(7):1673–7.

28. Bytzer P, Morocutti A, Kennerly P, et al. Effect of rabeprazole and omeprazole on the onset of gastro-oesophageal reflux disease symptom relief during the first seven days of treatment. *Scand J Gastroenterol*. 2006 Oct;41(10): 1132–40.

29. Holtmann G, Bytzer P, Metz M, et al. A randomized, double-blind, comparative study of standard-dose rabeprazole and high-dose omeprazole in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2002 Mar;16(3): 479–85.

30. Pace F, Annese V, Prada A, et al. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. *Dig Liver Dis*. 2005 Oct;37(10): 741–50.

31. Delchier JC, Cohen G, Humphries TJ. Rabeprazole, 20 mg once daily or 10 mg twice daily, is equivalent to omeprazole, 20 mg once daily, in the healing of erosive gastro-oesophageal reflux disease. *Scand J Gastroenterol*. 2000 Dec;35(12):1245–50.

32. Dekkers CP, Beker JA, Thjodleifsson B, et al. Double-blind, placebo-controlled comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. The European Rabeprazole Study Group. *Aliment Pharmacol Ther*. 1999 Jan;13(1):49–57.

33. Pilotto A, Franceschi M, Leandro G, et al. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. *World J Gastroenterol*. 2007 Sep 7;13(33):4467–72.

34. Birbara C, Breiter J, Perdomo C, et al. Rabeprazole for the prevention of recurrent erosive or ulcerative gastro-oesophageal reflux disease. Rabeprazole Study Group. *Eur J Gastroenterol Hepatol*. 2000 Aug;12(8):889–97.

35. Caos A, Moskovitz M, Dayal Y, et al. Rabeprazole for the prevention of pathologic and symptomatic relapse of erosive or ulcerative gastro-oesophageal reflux disease. Rebeprazole Study Group. *Am J Gastroenterol*. 2000 Nov;95(11):3081–8.

36. Caos A, Breiter J, Perdomo C, et al. Long-term prevention of erosive or ulcerative gastro-oesophageal reflux disease relapse with rabeprazole 10 or 20 mg vs. placebo: results of a 5-year study in the United States. *Aliment Pharmacol Ther*. 2005 Aug 1;22(3):193–202.

37. Thjodleifsson B, Rindi G, Fiocca R, et al. 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 Feb;17(3):343–51.

38. Kusano M, Shirai N, Yamaguchi K, et al. It is possible to classify non-erosive reflux disease (NERD) patients into endoscopically normal groups and minimal change groups by subjective symptoms and responsiveness to rabeprazole—a report from a study with Japanese patients. *Dig Dis Sci*. 2008 Dec;53(12):3082–94.

39. Fock KM, Teo EK, Ang TL, et al. Rabeprazole vs. esomeprazole in non-erosive gastro-esophageal reflux disease: a randomized, double-blind study in urban Asia. *World J Gastroenterol*. 2005 May 28;11(20):3091–8.

40. Miner P Jr, Orr W, Filippone J, et al. Rabeprazole in nonerosive gastroesophageal reflux disease: a randomized placebo-controlled trial. *Am J Gastroenterol*. 2002 Jun;97(6):1332–9.

41. Morgan DG, O'Mahony MF, O'Mahony WF, et al. RAB-GRD-3002 Study Group. Maintenance treatment of gastroesophageal reflux disease: an evaluation of continuous and on-demand therapy with rabeprazole 20 mg. *Can J Gastroenterol*. 2007 Dec;21(12):820–6.

42. Eggleston A, Katelaris PH, Nandurkar S, et al. Clinical trial: the treatment of gastro-oesophageal reflux disease in primary care-prospective randomized comparison of rabeprazole 20 mg with esomeprazole 20 and 40 mg. *Aliment Pharmacol Ther*. 2009 May 1;29(9):967–78.

43. Ariizumi K, Ohara S, Koike T, et al. Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. *J Gastroenterol Hepatol*. 2006 Sep;21(9): 1428–34.

44. Kahrilas PJ, Miner P, Johanson J, et al. Efficacy of rabeprazole in the treatment of symptomatic gastroesophageal reflux disease. *Dig Dis Sci*. 2005 Nov;50(11):2009–18.

45. Metz DC, Inadomi JM, Howden CW, et al. On-demand therapy for gastroesophageal reflux disease. *Am J Gastroenterol*. 2007 Mar;102(3):642–53.

46. Sugawa T, Fujiwara Y, Yamagami H, et al. A novel rat model to determine interaction between reflux oesophagitis and bronchial asthma. *Gut*. 2008 May;57(5):575–81.

47. Tsugeno H, Mizuno M, Fujiki S, et al. A proton-pump inhibitor, rabeprazole, improves ventilatory function in patients with asthma associated with gastroesophageal reflux. *Scand J Gastroenterol*. 2003 May;38(5): 456–61.

48. Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA*. 2005 Sep 28;294(12):1534–40.

49. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope*. 1991 Apr;101(4 Pt 2 Suppl 53):1–78.

50. Oridate N, Takeda H, Mesuda Y, et al. Evaluation of upper abdominal symptoms using the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease in patients with laryngopharyngeal reflux symptoms. *J Gastroenterol*. 2008;43(7):519–23.

51. Dickman R, Emmons S, Cui H, et al. The effect of a therapeutic trial of high-dose rabeprazole on symptom response of patients with non-cardiac chest pain: a randomized, double-blind, placebo-controlled, crossover trial. *Aliment Pharmacol Ther*. 2005 Sep 15;22(6):547–55.

52. Kim JH, Sinn DH, Son HJ, et al. Comparison of one-week and two-week empirical trial with a high-dose rabeprazole in non-cardiac chest pain patients. *J Gastroenterol Hepatol*. 2009 Sep;24(9):1504–9.

53. Fujiwara Y, Kohata Y, Kaji M, et al. Sleep dysfunction in Japanese patients with gastroesophageal reflux disease: prevalence, risk factors, and efficacy of rabeprazole. *Digestion*. 2010;81(3):135–41.

54. Ji S, Kim HS, Kim JW, Jee MK, et al. Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. *J Gastroenterol Hepatol*. 2006 Sep;21(9):1381–7.

55. Dekkers CP, Beker JA, Thjodleifsson B, et al. Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of active gastric ulcer-a European multicentre study. The European Rabeprazole Study Group. *Aliment Pharmacol Ther*. 1998 Aug;12(8):789–95.

56. Dekkers CP, Beker JA, Thjodleifsson B, et al. Comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of active duodenal ulcer: a European multicentre study. *Aliment Pharmacol Ther*. 1999 Feb;13(2):179–86.

57. Ando T, Kato H, Sugimoto N, et al. A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. *Dig Dis Sci*. 2005 Sep;50(9):1625–31.

58. Laine L, Bombardier C, Hawkey CJ, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology*. 2002 Oct;123(4):z1006–12.

59. Sugimoto M, Nishino M, Kodaira C, et al. Esophageal mucosal injury with low-dose aspirin and its prevention by rabeprazole. *J Clin Pharmacol*. 2010 Mar;50(3):320–30.

60. Nishino M, Sugimoto M, Kodaira C, et al. Relationship between low-dose aspirin-induced gastric mucosal injury and intragastric pH in healthy volunteers. *Dig Dis Sci*. 2009 Aug 12. [Epub ahead of print].

61. Mizokami Y. Efficacy and safety of rabeprazole in non-steroidal anti-inflammatory drug-induced ulcer in Japan. *World J Gastroenterol*. 2009 Oct 28; 15(40):5097–102.

62. Green FW Jr, Kaplan MM, Curtis LE, et al. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor to prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology*. 1978 Jan; 74(1):38–43.

63. Kolkman JJ, Meuwissen SG. A review on treatment of bleeding peptic ulcer: a collaborative task of gastroenterologist and surgeon. *Scand J Gastroenterol Suppl*. 1996;218:16–25.

64. Brunner G, Luna P, Thiesemann C. Drugs for pH control in upper gastrointestinal bleeding. *Aliment Pharmacol Ther*. 1995;9 Suppl 1:47–50.

65. Uedo N, Takeuchi Y, Yamada T, et al. Effect of a proton pump inhibitor or an H2-receptor antagonist on prevention of bleeding from ulcer after endoscopic submucosal dissection of early gastric cancer: a prospective randomized controlled trial. *Am J Gastroenterol*. 2007 Aug;102(8):1610–6.

66. Morocutti A, Merrouche M, Bjaaland T, Humphries T, Mignon M. An open-label study of rabeprazole in patients with Zollinger-Ellison syndrome or idiopathic gastric acid hypersecretion. *Aliment Pharmacol Ther*. 2006 Nov 15;24(10):1439–44.

67. Gisbert JP. Potent gastric acid inhibition in Helicobacter pylori eradication. *Drugs*. 2005;65 Suppl 1:83–96.

68. Kawakami Y, Akahane T, Yamaguchi M, et al. In vitro activities of rabeprazole, a novel proton pump inhibitor, and its thioether derivative alone and in combination with other antimicrobials against recent clinical isolates of Helicobacter pylori. *Antimicrob Agents Chemother*. 2000 Feb;44(2): 458–61.

69. Choi HS, Park DI, Hwang SJ, et al. Double-dose, new-generation proton pump inhibitors do not improve Helicobacter pylori eradication rate. *Helicobacter*. 2007 Dec;12(6):638–42.

70. Hawkey CJ, Atherton JC, Treichel HC, et al. Safety and efficacy of 7-day rabeprazole- and omeprazole-based triple therapy regimens for the eradication of Helicobacter pylori in patients with documented peptic ulcer disease. *Aliment Pharmacol Ther*. 2003 Apr;17(8):1065–74.

71. Wu IC, Wu DC, Hsu PI, et al. Rabeprazole- versus esomeprazole-based eradication regimens for *H. pylori* infection. *Helicobacter*. 2007 Dec;12(6): 633–7.

72. Murakami K, Sato R, Okimoto T, et al. Eradication rates of clarithromycin-resistant Helicobacter pylori using either rabeprazole or lansoprazole plus amoxicillin and clarithromycin. *Aliment Pharmacol Ther*. 2002 Nov;16(11): 1933–8.

73. Robinson M. Proton pump inhibitors: update on their role in acid-related gastrointestinal diseases. *Int J Clin Pract*. 2005 Jun;59(6):709–15.

74. Talley NJ, Vakil N; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. *Am J Gastroenterol*. 2005 Oct;100(10):2324–37.

75. Peura DA, Gudmundson J, Siepman N, et al. Proton pump inhibitors: effective first-line treatment for management of dyspepsia. *Dig Dis Sci*. 2007 Apr; 52(4):983–7.

76. Grudell AB, Camilleri M, Burton DD, et al. Effect of a proton pump inhibitor on postprandial gastric volume, emptying and symptoms in healthy human subjects: a pilot study. *Aliment Pharmacol Ther*. 2006 Oct 1;24(7): 1037–43.

77. Kamiya T, Hirako M, Shikano M, et al. Rabeprazole vs. itopride: a randomized multicenter trial to determine efficacy in functional dyspepsia in Japan. *Gastroenterology*. 2008;134(4 Suppl 1):A630, W1084, Abstract.

78. Kamiya T, Shikano M, Hirako M, et al. Rabeprazole vs. itopride: a randomized, multicenter trial in Nagoya to determine efficacy in Japanese patients with functional dyspepsia. *Gastroenterology*. 2009;136(5 Suppl 1):A181–2, S1068, Abstract.

79. Tominaga K, The CAESAR Study Group, et al. Rabeprazole improves the symptoms of functional dyspepsia—a double-blind randomized placebo-controlled multi-center trial in Japan: the CAESAR study. *Gastroenterology*. 2010;138 Suppl 1:383, Abstract (http://download.abstractcentral.com/DDW2010/myddw/383.html).