Rabeprazole and esomeprazole in mild-to-moderate erosive gastroesophageal reflux disease: A comparative study of efficacy and safety

Rituparna Maiti, Jyothirmai Jaida, P. L. John Israel[1], Narendar Koyagura, Sruthi Mukkisa, Anuradha Palani

Departments of Pharmacology and [1]General Medicine, Prathima Institute of Medical Sciences, Nagunur Road, Karimnagar, Andhra Pradesh, India

ABSTRACT

Objective: To compare the efficacy and safety of rabeprazole and esomeprazole in mild-to-moderate erosive gastroesophageal reflux disease (GERD). **Materials and Methods:** A randomized, single-blinded, outdoor-based clinical study was conducted on 60 patients of mild-to-moderate erosive GERD. After baseline clinical assessment and investigations, rabeprazole (40 mg) was prescribed to 30 patients and esomeprazole (40 mg) to another 30 patients for 4 weeks. The efficacy variables were change in GERD symptom scoring, endoscopic findings, and Quality of Life in Reflux and Dyspepsia (QOLRAD) scoring over 4 weeks. **Result:** Heartburn, acid regurgitation, and overall GERD symptom scoring (P = 0.01) were significantly decreased with rabeprazole in comparison to esomeprazole. The comparative study of all five domains of the QOLARD questionnaire including overall scoring revealed a statistically significant improvement in the rabeprazole group. Endoscopic findings in the rabeprazole group showed an absolute improvement of 30% and relative improvement of 55% over esomeprazole. Both the drugs were well tolerated having no significant difference in the incidence of adverse effects. **Conclusion:** Rabeprazole (40 mg) is a better choice for mild-to-moderate GERD compared with esomeprazole (40 mg) because of its better efficacy and safety profile.

Key words: Gastroesophageal reflux disease, gastroesophageal reflux disease symptom scoring, Quality of Life in Reflux and Dyspepsia scoring, rabeprazole, esomeprazole

INTRODUCTION

Gastroesophageal reflux disease (GERD) is characterized by recurrent regurgitation into the esophagus, causing heartburn, chest pain, and dysphagia. GERD is a highly prevalent (10–20% of the population) condition having a significant impact on the quality of life leading to high healthcare expenditures.[1,2] GERD patients may be categorized according to their symptoms and endoscopic findings. From an endoscopic point of view, GERD patients are classified as those with no recognizable esophageal erosion (nonerosive reflux disease, NERD), those with visible distal esophageal erosions (erosive reflux disease, ERD), and those with columnar metaplasia in the distal esophagus (Barrett's esophagus, BE).[3] Though the etiopathogenesis of the disease is multifactorial, the main attributing factor is the dysfunction of the lower esophageal sphincter.[4-6]

Address for correspondence:
Rituparna Maiti, Department of Pharmacology, Prathima Institute of Medical Sciences, Nagunur Road, Karimnagar, Andhra Pradesh, India.
E-mail: rituparnamaiti@rediffmail.com

Ensuring relief of symptoms in patients with GERD is an important treatment goal. The ideal treatment should improve patients' quality of life by providing rapid relief of symptoms and reducing the severity and number of recurrent episodes.[7] Proton pump inhibitors (PPIs) are the most effective drugs to control GERD symptoms, and to cure esophagitis endoscopically.[8,9] PPIs such as omeprazole, esomeprazole, lansoprazole, and rabeprazole effectively inhibit the duration and extent of gastric acid secretion and provide more complete remission of the symptoms of heartburn than other antisecretory drugs.[10,11] However, the response to PPIs in patients with nonerosive reflux disorder is less efficacious when compared to patients with erosive GERD.[12]

Two new PPIs, rabeprazole and esomeprazole, have been already proved to be effective and safe in GERD. Rabeprazole is a PPI that effectively provides symptom relief and healing, and prevents relapse, in patients with erosive GERD. Esomeprazole, the s-enantiomer of omeprazole, has demonstrated superior efficacy over omeprazole in healing and symptom resolution in patients with erosive and nonerosive reflux disease.[13,14] Currently, the market is flooded with "me-too" drugs and physicians are inundated with the promotional literature from pharmaceutical companies. So our present study is an effort to determine the better agent between rabeprazole and esomeprazole in mild-to-moderate erosive GERD.

MATERIALS AND METHODS

Patients

The study was conducted on 60 patients of mild-to-moderate erosive gastroesophageal disease attending the outdoor department of General Medicine, Prathima Institute of Medical Sciences, Karimnagar, Andhra Pradesh, India. The study population included patients, irrespective of sex, aged 18–65 years suffering from GERD symptoms for at least 3 months in the previous year. Subjects experienced at least one period of moderate-to-severe heartburn or regurgitation in the past 7 days prior to treatment and at endoscopy; they had grade A or grade B esophagitis according to the Los Angeles (LA) classification. Patients were excluded for the following reasons: known history of gastroduodenal ulcer; infectious or inflammatory conditions of the intestine (including inflammatory bowel disease); malabsorption syndromes; obstruction; gastrointestinal malignancy; gastric or intestinal surgery including vagotomy; Barrett's esophagus; esophageal stricture or pyloric stenosis; scleroderma; pregnancy; abnormal laboratory tests at the initial visit (including liver enzymes greater than twice the upper limit of normal); GERD treatment refractory to a 2-month course of H_2-blocker or PPI therapy; PPIs taken within 14 days of screening or H_2-blocker or prokinetic agent taken within 7 days of screening; daily

use of NSAIDs, oral steroids, aspirin (>325 mg/day); being unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates, or sucralfate.

Study design

The present study is a 4-week, randomized, single-blinded, parallel group comparative clinical study between rabeprazole and esomeprazole in patients with mild-to-moderate erosive GERD conducted in a single center. The study was approved by the institute ethics committee. A written informed consent was taken from all the patients participating in the study after explaining the patient's diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of a proposed treatment (rabeprazole/esomeprazole), alternative treatment, and the risks and benefits of the alternative treatment. Randomization was done by using a computer-generated random list. After randomization, the patients were divided into two treatment groups. A total of 30 patients were allocated in the rabeprazole group who received rabeprazole 40 mg daily and another 30 patients in the esomeprazole group who received esomeprazole 40 mg daily for 4 weeks. [Figure 1] The patients received the drugs free of cost from our institute pharmacy. At the first visit, after a detailed history was taken on baseline symptomatology, clinical evaluation [including GERD symptom score and quality of life in reflux and dyspepsia (QOLRAD) scoring] and laboratory investigations (upper GI endoscopy, liver function test) were done. After 4 weeks, upper GI endoscopy was repeated and the clinical improvement was assessed in terms of the change in endoscopic findings, GERD symptom score, and QOLRAD scoring. The liver function test was done for all follow-up patients at the second visit to detect any hepatic dysfunction.

Efficacy and safety variables

The efficacy variables were changes from baseline to day 28 in the severity of GERD symptoms based on GERD symptom scoring, endoscopic findings, and QOLRAD scoring.

The improvement in the four most important GERD symptoms (heartburn, acid regurgitation, epigastric distress, and dysphagia) have been scored on a scale of 0–4 depending on severity to assess the efficacy of the candidate drugs. The symptom severity was defined as follows: 0 = no symptoms; 1 = mild (symptoms are present occasionally and patients can continue with daily activities); 2 = moderate (symptoms are present most of the time but patients can perform daily activities); 3 = severe (symptoms are present continuously. The symptoms are severe and affect daily activities or patient cannot do things that they normally can); 4 = very severe (symptoms are so severe that the patient has to stay in bed and cannot perform activities that one normally could).[15,16]

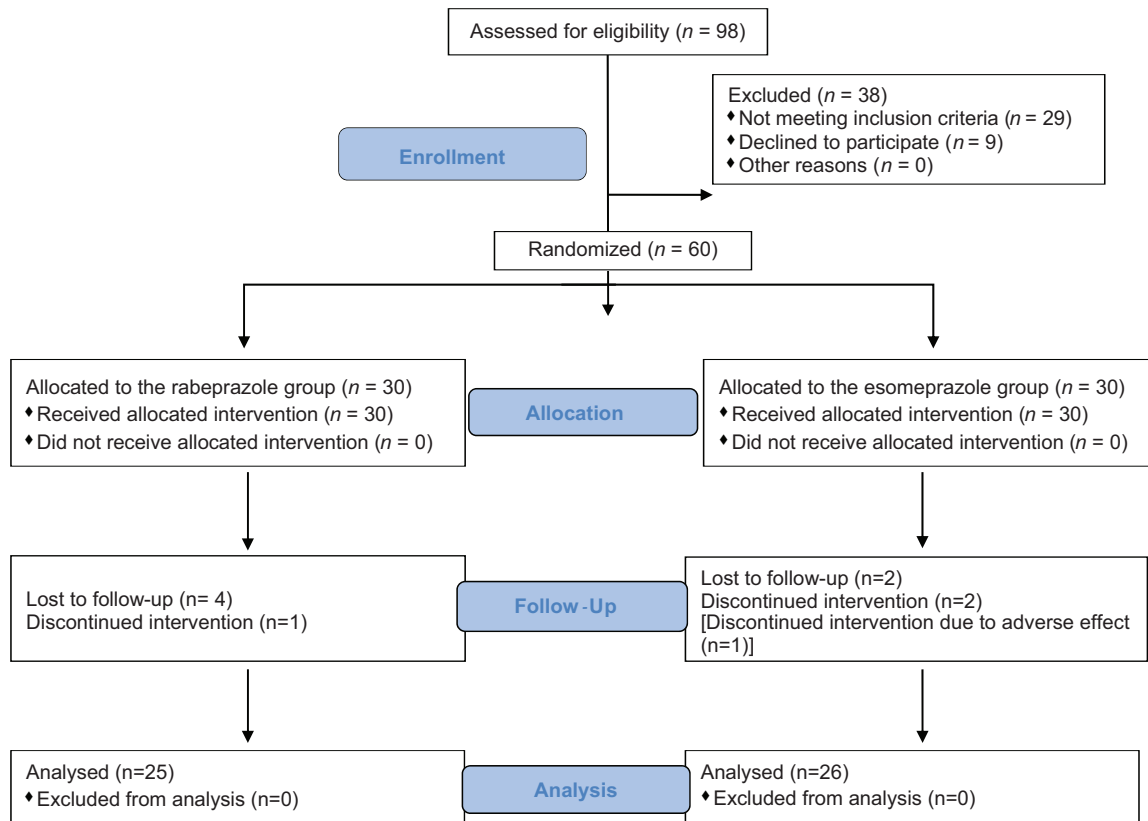The QOLRAD questionnaire is a disease-specific instrument, including 25 items combined into five dimensions: emotional

Figure 1: Recruitment, allocation and follow-up of participants

distress, sleep disturbance, vitality, food/drink problems, and physical/social functioning. The dimensions include the following items by domain – emotional distress: discouraged or distressed, frustrated or impatient, anxious or upset, worries or fears, irritable, and the exact cause is not known; sleep disturbance: tired due to the lack of sleep, waking at night, fresh and rested, and trouble getting to sleep; vitality: feeling tired or worn out, generally unwell, and lack of energy; food/drink problems: eat less than usual, unable to eat foods or snacks, food unappealing, not tolerating food or snacks, and avoiding certain food/drink; physical/social functioning: avoid bending over, doing things with family, difficulty in socializing, unable to carry out daily activities, and unable to carry out physical activities. All questions are rated on a seven-point Likert scale according to the following response options: all of the time, most of the time, quite a lot of the time, some of the time, a little of the time, hardly any of the time, none of the time; for questions 3, 16, and 19, the responses were a great deal, a lot, a moderate amount, some, a little, hardly any, none at all. The lower was the value, the more severe the impact on daily function was. QOLRAD scoring has been extensively documented in international studies in patients of heartburn with regard to reliability, validity, and responsiveness to change.[17,18]

One of the most commonly used classification systems for endoscopic GERD is the LA classification. Developers of the LA classification tried to avoid subjective interpretations and relied on objective criteria to make the diagnosis of endoscopic GERD. Finding a definite break in the mucosa called "erosion" is essential to diagnose endoscopic GERD in the LA classification. Depending on the length of the erosion and its extension between esophageal folds, different grades are assigned.[19] In this study, patients who were suffering from grade A (erosion, 5 mm or less, not extending between folds) or grade B (erosions more than 5 mm, not extending between the folds) oesophagitis were included.

Tolerability was assessed in terms of reported adverse experiences and vital signs, which were measured at baseline and at the end of the study. All reported adverse drug reactions were graded according to the National Cancer Institute Common Toxicity Criteria (CTC) and compared between the groups.

Statistical analysis
Statistical analysis was carried out using the paired *t*-test, unpaired *t*-test, and Fisher's exact test. $P < 0.05$ was considered statistically significant. Considering the GERD symptom score as the primary outcome, the sample size has been calculated taking the level of significance (α) as 0.05, power of the study $(1 - \beta)$ as 0.85, and expected mean difference as 1.25.

RESULTS

Patient disposition and baseline demographics

A total of 60 patients were randomized to two groups to receive either rabeprazole ($n = 30$) or esomeprazole ($n = 30$). Postbaseline values were missing in nine patients (five in the rabeprazole group and four in the esomeprazole group) because they were lost to follow-up due to noncompliance ($n = 8$) or adverse effect ($n = 1$). [Figure 1] The treatment groups were comparable in demographic features and baseline clinical characteristics [Table 1]. The age of the patients ranged from 18 to 65 years (mean age, 38 years in the rabeprazole group and 35 years in the esomeprazole group), and 38% were female and 62% male. The mean duration of GERD symptoms was 15 weeks in the rabeprazole group and 14 weeks in the esomeprazole group.

Efficacy analysis
Change in GERD symptoms

The improvement in the four most important GERD symptoms (heartburn, acid regurgitation, epigastric distress, and dysphagia) has been scored on a scale of 0–4 depending on severity to assess the efficacy of the candidate drugs. Rabeprazole and esomeprazole have been found to decrease heartburn and acid regurgitation significantly in their respective groups and when the percentage changes have been compared, rabeprazole has been found to be superior to esomeprazole in controlling those symptoms. Epigastric distress and dysphagia were found to decrease significantly in both groups but the change in the rabeprazole group was not statistically significant when compared to the esomeprazole group. The improvement in the overall symptom score was significantly lower in both groups, and rabeprazole ($P = 0.01$) was found to be superior over esomeprazole when compared by the *t*-test [Table 2].

Change in the QOLRAD scoring

In this study, improvement has been seen in all five domains with both the drugs. But the improvement with rabeprazole was found to be more in comparison to esomeprazole over 1 month. In the rabeprazole group, the percentage change in emotional distress (37.2%), sleep disturbance (46.4%), food/drink problems (43.7%), and vitality (40.5%) questionnaire scoring was found to be significantly different when compared to esomeprazole group. But the change in the physical/social function questionnaire scoring in the rabeprazole group (39%) was not significant in the esomeprazole group (17.6%). An increase in the overall score of QOLRAD was also found to be statistically significant in the rabeprazole group ($P < 0.0001$). [Table 2]

Change in endoscopic findings

At endoscopy, the patients having grade A or grade B GERD according to the LA classification were recruited. Endoscopy was done both at the first and second visit. In the rabeprazole group, 22 patients were diagnosed to have grade A GERD and in the esomeprazole group, 18 patients had grade A GERD. The rest of the patients had grade B GERD. After 1-month treatment, in the rabeprazole group, 21 patients showed improvement whereas in the esomeprazole group, 14 patients showed endoscopic improvement. The endoscopic findings and analysis of risk reduction have been summarized in Table 3. The endoscopic findings have also been presented in 2 × 2

Table 1: Baseline demographic data and clinical characteristics of 60 patients of mild-to-moderate erosive GERD participated in the study in the first visit

Characteristics	Rabeprazole group	Esomeprazole group	*P*-value
Number of patients recruited	30	30	
Number of patients at follow-up	25	26	
Female sex (%)	36.7	43.3	0.47
Age (years)	38 ± 11.7	35.3 ± 11.8	0.38
Duration of GERD (weeks)	15.1 ± 0.7	13.7 ± 10.0	0.62
Heartburn symptom scoring	1.57 ± 0.7	1.73 ± 1.1	0.49
Acid regurgitation symptom scoring	1.40 ± 0.6	1.37 ± 0.8	0.86
Epigastric distress symptom scoring	1.23 ± 0.8	1.03 ± 0.9	0.34
Dysphagia symptom scoring	0.40 ± 0.5	0.53 ± 0.6	0.37
GERD symptom scoring (overall)	4.6 ± 1.8	4.7 ± 2.2	0.89
Emotional distress scoring	8.77 ± 5.6	7.43 ± 3.5	0.27
Sleep disturbance scoring	7.93 ± 4.7	8.53 ± 5.7	0.66
Food/drink problems scoring	7.3 ± 5.5	6.9 ± 5.3	0.81
Physical/social function scoring	7.8 ± 5.7	6.4 ± 5.5	0.35
Vitality scoring	6.9 ± 3.8	5.8 ± 3.6	0.23
QOLRAD questionnaire scoring (overall)	38.7 ± 14.8	35.1 ± 12.8	0.32
Endoscopic finding (LA classification)	73.3	60	0.41
Stage A (%)			
H. pylori positive cases	12/30	14/30	0.79

The values are mean ± SD, GERD: Gastroesophageal reflux disease.

Table 2: Change in GERD symptom scoring and QOLRAD questionnaire scoring in follow-up patients (*n* = 51) after 4 weeks

Variable		Rabeprazole group (*n* = 25)				Esomeprazole group (*n* = 26)				Difference between the groups (% change in Rabeprazole group vs. % change in Esomeprazole)
		1st Visit	2nd Visit	% Change	*P*-value (1st vs. 2nd visit)	1st Visit	2nd Visit	% Change	*P*-value (1st vs. 2nd visit)	
GERD symptom scoring	Heartburn symptom scoring	1.52 ± 0.7	1.0 ± 0.6	34.2	<0.001	1.69 ± 1.1	1.35 ± 0.75	20.1	0.001	0.017
	Acid regurgitation symptom scoring	1.40 ± 0.6	0.92 ± 0.6	34.3	0.001	1.35 ± 0.8	1.03 ± 0.5	23.7	0.003	0.03
	Epigastric distress symptom scoring	1.16 ± 0.8	0.76 ± 0.5	34.5	0.005	0.92 ± 0.8	0.69 ± 0.6	25	0.01	0.33
	Dysphagia symptom scoring	0.40 ± 0.6	0.12 ± 0.3	70	0.005	0.46 ± 0.6	0.27 ± 0.5	41.3	0.02	0.44
	Symptom scoring (overall)	4.5 ± 1.8	2.8 ± 1.4	37.8	<0.001	4.4 ± 2.2	3.3 ± 1.6	25	<0.001	0.01
QOLRAD questionnaire scoring	Emotional distress scoring	9.04 ± 5.5	12.4 ± 4.8	37.2	<0.001	6.73 ± 3.0	7.5 ± 2.7	11.4	0.04	0.017
	Sleep disturbance scoring	7.24 ± 4.0	10.6 ± 4.9	46.4	<0.001	8.69 ± 5.8	9.58 ± 5.6	10.2	0.02	0.001
	Food/drink problems scoring	6.96 ± 5.1	10.0 ± 5.5	43.7	<0.001	7.15 ± 5.6	8.0 ± 5.7	11.9	0.005	0.002
	Physical/social function scoring	7.84 ± 5.9	10.9 ± 5.84	39.0	<0.001	6.08 ± 5.5	7.15 ± 4.8	17.6	0.003	0.17
	Vitality scoring	6.92 ± 3.9	9.72 ± 5.4	40.5	<0.001	5.85 ± 3.6	6.61 ± 3.7	12.9	0.03	0.003
	QOLRAD questionnaire scoring (overall)	38.0 ± 13.6	53.7 ± 14.4	41.3	<0.001	34.5 ± 13.4	38.9 ± 12.5	12.8	<0.001	<0.001

The values are mean ± SD, GERD: Gastroesophageal reflux disease; QOLRAD: Quality of Life in Reflux and Dyspepsia

contingency table and statistical significance has been tested by Fisher's exact test ($P = 0.03$). A *P*-value < 0.05 indicates that the change in the rabeprazole group is statistically significant and not by random occurrence.

Endoscopy showed that the incidence of residual esophagitis after 4 weeks was higher in the esomeprazole group compared to the rabeprazole group [Table 3]. Similarly, the incidence of healing was significantly higher ($P = 0.03$) in the rabeprazole group compared to the esomeprazole group. This represents an absolute improvement of 30% and relative improvement of 55% over esomeprazole, yielding an NNT (number of patients needed to treat to benefit at least one patient) of only 3 patients.

In our study groups, there was no significant baseline difference in the *Helicobacter pylori* status [Table 1]. The postdrug *H. pylori* status was also not significantly affected by either rabeprazole or esomeprazole [Table 3].

Safety analysis

Both the drugs were well tolerated. In the rabeprazole group, out of four patients who experienced adverse effects, two complained of headache, one had dizziness, and one patient showed a borderline increase in serum AST/ALT. In the esomeprazole group, two patients complained of headache, one patient had nausea, one patient had diarrhea, and in two patients there was a borderline increase in AST/ALT. According to the CTC grading of adverse drug reactions, all the reported side effects were of grade 1 (mild) except in one patient. One patient of the esomeprazole group, who complained of moderate, persistent headache, discontinued the treatment and was excluded from the study.

The overall incidence of adverse effects was 16% and 23.1% in the rabeprazole and esomeprazole group, respectively. To compare the incidence of adverse effects of two groups, Fisher's exact test was done and it was found to be statistically nonsignificant ($P = 0.72$).

DISCUSSION

The goal of treatment of GERD is to improve patients' quality of life by providing rapid relief of symptoms and reducing the

Table 3: Endoscopic findings

Parameters	1st Visit		2nd Visit		Analysis of findings				
	Rabeprazole group	Esomeprazole group	Rabeprazole group	Esomeprazole group	CER	TER	ARR	RRR	NNT
Patients with esophagitis	25	26	10	17	0.65	0.40	25%	38%	4
Grade A	22	18	9	13					
Grade B	3	8	1	4					
Investigator-reported improvement in endoscopic findings and healing									
Improvement	NA	NA	21	14	0.54	0.84	30%	55%	3
No improvement	NA	NA	4	12					
H. pylori status									
H. pylori positive cases	10/25	13/26	7/25	9/26	Analyzed by Fisher's test: 1st visit: *P* = 0.58 2nd visit: *P* = 0.76				

CER: Control event rate; TER: Test event rate; ARR: Absolute risk reduction; RRR: Relative risk reduction; NNT: Number needed to treat

severity and number of recurrent episodes and this is measured as improvement of GERD symptoms scores, especially of heartburn or acid regurgitation. In this study, rabeprazole and esomeprazole have been found to decrease heartburn and acid regurgitation significantly in their respective groups and when the percentage changes were compared, rabeprazole has been found to be superior to esomeprazole in controlling those symptoms. The improvement in the overall symptom score was significantly lowered in both groups and rabeprazole was found to be superior over esomeprazole when compared by the *t*-test. The present study supports the findings of a previous study by Warrington *et al.* where rabeprazole was found to be a better antisecretory agent than esomeprazole.[20] In this study, improvement was seen in all five domains of QOLRAD scoring with both the drugs. But the improvement with rabeprazole was found to be more than esomeprazole over 1 month. So in all five domains, rabeprazole was found to be superior to esomeprazole in reducing the impact on daily functioning and improving quality of life. An increase in the overall score of QOLRAD was also found to be statistically significant in the rabeprazole group. The changes in the esomeprazole group of our study are close to those of the previous studies done by Gunasekaran *et al.* and Attwood *et al.*[21,22] Endoscopic findings showed that the incidence of residual esophagitis after 4 weeks was higher in the esomeprazole group compared to the rabeprazole group. Similarly, the incidence of healing and percentage risk reduction was significantly higher in the rabeprazole group compared to the esomeprazole group. Like other PPIs, both rabeprazole and esomeprazole were well tolerated without any severe side effects. The previous studies by Fock *et al.* and Pai *et al.* also reported the safety of these drugs.[15,23]

The superiority of rabeprazole over esomeprazole found in our study has been supported by a comparative study where rabeprazole 20 mg daily was found to be more effective than esomeprazole 20 mg daily in increasing intragastric pH and maintaining pH > 3 and >4. On day 5, mean pH AUC was higher after esomeprazole than rabeprazole.[20] A previous study by Caos *et al* demonstrated the safety and efficacy of 20 and 10 mg rabeprazole in maintaining GERD healing for up to 5 years compared to placebo. Both doses were effective in preventing the relapse of GERD, heartburn frequency, and daytime heartburn severity, with the 20-mg dose also effective in preventing night time heartburn severity. Rabeprazole treatment improved patients' quality of life when compared to placebo. Both rabeprazole doses were well tolerated and equally safe.[24] In providing rapid, sustained acid control, rabeprazole effectively relieves the symptoms of GERD and has been shown to be effective for acute healing of erosive esophagitis and 1-year maintenance of healing. In another study, rabeprazole increased intragastric pH with a rapid onset of action (within hours) and maintained an elevated pH through and between meals. This effect was seen on the first day and maintained throughout 8 days of rabeprazole treatment.[25] Rabeprazole was demonstrated to be superior to omeprazole on the first treatment day, by maintaining a higher diurnal and nocturnal gastric pH at half dosage and decreasing more deeply the gastric acidity at full dosage (rabeprazole: 66%, omeprazole: 35%).[26-28]

Several mechanisms may explain the superior efficacy of rabeprazole in increasing the intragastric pH and decreasing the acid output. Rates of acid inhibition are known to correlate with the acid stability of PPIs. Rabeprazole, which has the highest pKa of all PPIs and is therefore least stable at neutral pH, is more rapidly converted to inhibit the proton pump as compared to omeprazole, lansoprazole, or pantoprazole.[29] This may be critical given the known short half-lives of PPIs that limit time available to accumulate in the parietal canaliculus, to form the activated sulphenamide form, and to bind to inactivate proton pumps.[28] In addition, rabeprazole may have more prolonged and potent acid inhibitory effects due to continued binding to proton pump transmembrane domains even after achieving 100% inhibition of the ATPase activity.[30] While the majority of available parietal cells typically maintain an intracellular pH near 1, a proportion of these target cells may have a pH as high as 3 depending largely on the age of that cell. In extremely

acidic environments, PPIs may have similar equipotency.[31] However, in less acidic environments, rabeprazole, given its rapid activation over a wide pH range, actually targets a greater population of parietal cells to give a more rapid and pronounced degree of acid inhibition.[32] In older parietal cells, rabeprazole can be as much as 10 times more potent than other PPIs.[31] In addition, rabeprazole has an advantage not shared by other PPIs. Its metabolism is largely nonenzymatic and therefore less dependent on CYP2C19, giving a greater consistency of pharmacokinetics across all patients, regardless of the CYP2C19 genotype.[33]

CONCLUSIONS

From the results of the present comparative clinical analysis of rabeprazole and esomeprazole, we conclude that rabeprazole (40 mg) is a better choice in mild-to-moderate erosive GERD compared with esomeprazole (40 mg) owing to its better efficacy and safety profile. This study has limitations because of being a single-blinded and single-center study, and hence the findings of this exploratory study should be confirmed by multicentric, randomized, double-blind, large population studies.

ACKNOWLEDGMENTS

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