Original Article

Efficacy and Safety of Rabeprazole versus Esomeprazole in mild to moderate Gastroesophageal Reflux Disease – A Prospective Comparative Study.

Indra.A[1], Rajaram.S[2], Ramya.R[3]

[1]General physician, Tanjore -613007,Tamilnadu.

[2] Professor, Department of Pharmacology,Vinayaka Mission's Kirupananda Variyar Medical College & hospitals,Vinayaka Mission's Research Foundation (DU),Salem -636308,Tamilnadu.

[3]Assistant professor,Department of Pharmacology,Vinayaka Missions Kirupananda Variyar Medical College & hospitals,Vinayaka Mission's Research Foundation (DU), Salem -636308,Tamilnadu.

Corresponding Author:
Dr.Ramya R, Assistant Professor, Department of Pharmacology, Vinayaka Mission's Kirupananda Variyar Medical College & hospitals, Vinayaka Mission's Research Foundation (DU), Salem, Tamilnadu.
Email id : ramyavishal1595@gmail.com Mobile : 8122170385

ABSTRACT

BACKGROUND:
Gastroesophageal reflux disease (GERD) is characterized by recurrent return of gastric contents back into the oesophagus causing heartburn, regurgitation and symptoms such as chest pain, coughing, hoarseness and dysphagia. The ideal treatment is to improve the patient's quality of life by providing rapid relief of symptoms and reducing the severity and number of recurrent episodes

OBJECTIVE: To compare the efficacy and safety of rabeprazole versus esomeprazole in mild to moderate GERD.

METHODS: This is a comparative study started with 60 patients with endoscopically proven GERD for at least 3 months before screening. Patients aged 25- 60yrs were randomly allocated into two groups. Group A received capsule Rabeprazole (20mg once daily) and group B received capsule Esomeprazole (40mg once daily) for 8 weeks. Follow-up was done on week 4 and 8. Assessment of improvement in 6point scale scoring and endoscopic findings were performed. Adverse events were recorded.

RESULT: In the study group of patients, about 32 were males and 28 were females. The mean reduction in pain scores of Rabeprazole at start of the study to 4 weeks and 8 weeks are 4.43 ± 0.679 to 1.87 ± 0.434, and 0.5 ± 0.630 when compared to Esomeprazole group - $4.43 \pm .626$ to 2.57 ± 0.568 and 0.83 ± 0.699 respectively. Even in the endoscopy findings above 90% of study subjects have normal endoscopic findings in the rabeprazole group but only 63% of study subjects have normal endoscopic findings.

CONCLUSION : Rabeprazole has better efficacy than Esomeprazole in mild to moderate GERD.

KEY WORDS : Rabeprazole, Esomeprazole, GERD

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is characterized by the recurrent return of gastric contents back into the oesophagus causing heartburn, regurgitation and symptoms such as chest pain, coughing, hoarseness and dysphagia[1,2].GERD symptoms can cause significant patient distress and can interfere with everyday life[2].The prevalence of GERD in India ranges from 8-20 percentages according to recently conducted studies based on different case definition and study methodology[3]. The ideal treatment is to improve the patient's quality of life by providing rapid relief of symptoms and reducing the severity and number of recurrent episodes[4]. Previous studies have shown that proton pump inhibitors (PPIs) are safer and more effective than H2 receptor antagonists in healing oesophageal lesions, relieving heartburn symptoms and preventing symptomatic and endoscopy relapse[5,6]. 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[7,8].

Esomeprazole is more effective for control of oesophageal and gastric acid than other PPIs. However, it is not more effective clinically except in patients with severe esophagitis.

Esomeprazole (S-omeprazole) is a single optical enantiomer PPI and the rational of developing this drug is its higher metabolic stability, which will lead to a higher bioavailability and increase in the area under the plasma concentration-time curve (AUC)[9].

Rabeprazole has the highest PKa of all PPIs and is therefore least stable at neutral PH and is more rapidly converted to inhibit the proton pump as compared to omeprazole, lansoprazole or pantaprazole[10]. This may be critical given the known short lives of PPIs that limit time available to accumulate in the parietal canaliculus, to form the activated sulphenamide form to bind to inactivate proton pumps. 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 ATPase activity[11]. Among four PPI Esomeprazole may be more effective than omeprazole, lanzoprazole and pantaprozole for the rapid relief of heartburn symptoms and acid reflux symptom in patient with GERD[12]. Rabeprazole effectively provides symptom relief and healing, and prevents relapse, in the patient with GERD [13,14]. Hence two drugs are selected to compare the efficacy and safety was planned.

ADVANTAGES OF RABEPRAZOLE

Rabeprazole has the highest pKa of all PPIs and the rapid formation of acid- activated rabeprazole is due to partly its higher pKa[15]. Rabeprazole achieved maximal inhibition within 8 mins of drug exposure[16]. 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)[17]. Rabeprazole has a rapid onset of action and achieves a maximal or near maximal effect[18]. In comparison with omeprazole, lansoprazole and pantoprazole, the pharmaco-dynamics of Rabeprazole are the least affected by cytochrome P450 (CYP)2C19 genotype[19]. Rabeprazole 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.[11]

NEED OF THE STUDY:

The several studies were conducted in foreign nations in different ethnic variations. There could be genetic variations in regards to pharmacokinetic and pharmacodynamics handling of the drugs by the body system. Cultural, environmental and lifestyle variations also could influence the results obtained in these studies. Hence an attempt has been made to evaluate the efficacy and safety of rabeprazole versus esomeprazole in Indian population.

OBJECTIVES

PRIMARY OBJECTIVE

To evaluate the efficacy of Esomeprazole with Rabeprazole in healing and symptomatic resolution of gastroesophageal reflux disease

SECONDARY OBJECTIVE

To compare the safety and tolerability of the above drugs in term of adverse drug monitoring

MATERIALS AND METHODS

This is a prospective comparative study. The treatment period was about 8 weeks in which 60 patients with endoscopically proven reflex esophagitis will be chosen in the Department of surgery. The study was carried out from March 2016 - March 2017 at the department of surgery, Vinayaka Mission's KirupanandaVariyar Medical College and Hospitals, salem.

Inclusion criteria : Both male and female patient with age between 30-60yrs with GERD symptoms (eg. heartburn, regurgitation) for at least 3 months before screening. Heartburn atleast 2 days/week for >1 month before screening endoscopy. Mild to moderate erosive GERD (LA grade C or D) at screening endoscopy. There was no restriction on baseline body mass index (BMI).

Exclusion Criteria: Known history of gastroduodenal ulcer, Infectious or inflammatory conditions of the intestine, Malabsorption syndromes, Obstruction, Gastrointestinal malignancy, Gastric or intestinalsurgery including vagotomy, Barrett's oesophagus, Oesophageal stricture or pyloric stenosis, Scleroderma, Pregnant and lactating women, Abnormal laboratory test at the initial visit – including liver enzymes greater than twice the upper limit of normal. GERD treatment refractory to a two month course of H2 blocker or PPI therapy, PPI taken within 14 days of screening or H2 blocker or Prokinetic agent taken within 7 days of screening, Daily use of NSAIDS, oral steroids, aspirin (>325mg /day), Being unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates or sucralfate.

Study design

Study was started after the protocol is approved by the Institutional ethical committee of Vinayaka Mission's Kirubananda Variyar Medical College, Salem. The patients attending the Surgery outpatient department with the history and clinical features suggestive of GERD will be selected and their endoscopy examination will be conducted. All endoscopic examinations were performed by one endoscopist, using a higher-resolution upper gastrointestinal endoscope before and 8 weeks after the administration of PPI. Endoscopic diagnosis and the grading of reflux esophagitis were based on Los Angeles classification[14].

After the selection, patients will be given thorough information about the purpose of the study and the drug used in the study. Laboratory parameters such as Haematology, Clinical biochemistry and Urine analysis are done. The patients who are willing to participate in the study is asked to fill up the informed consent after reading the Informed Consent Document and will be included in the study. After fulfilling the selection criteria, patients were randomised into two groups.

Group 1: Will be given C.Rabeprazole 20mg once daily1 hour before breakfast for 8 weeks

Group 2:Will be given C.Esomeprazole 40mg once daily 1 hour before breakfast for 8 weeks

All patients will be provided a symptom diary, in which the recordings of the severity of symptoms (heartburn and acid reflux) prior to and 8weeks of PPI administration. The severity of symptoms will be graded on 6point scale (0: none; 1: mild; 2: mild-moderate; 3: moderate ; 4: moderate-severe; 5: severe and / or intolerable) and to be recorded daily. Mild symptoms are defined as a heartburn/acid reflux that did not disturb the normal daily activity of the patients. Moderate symptoms were defined as those that bothered the daily activity, while the patients continued to work productively. Severe symptoms are those that stopped the daily productive activity of the patients.

The patients were instructed to record the severity of their symptoms as a whole previous day's score in the following morning.

STATISTICAL ANALYSIS

The data obtained was entered in Microsoft office excel and was analysed in SPSS 23. The basic Socio-demographic details and other basic information were described as frequencies and percentages with simple tables and bar diagram/pie chart. The association between different parameters at regular intervals were analysed using chi-square test and the results with their significance was presented.

RESULTS

Patient disposition

A total of 60 patients took part in the study, 30 receiving Rabeprazole and 30 receiving Esomeprazole. A total of 60 patients (100%) completed the study. None of the patients was withdrawn from the study untill the end of 8 weeks study period.

Demographic and baseline characteristics

Male and female populations are almost equally distributed among each group. Around 70% of study participants belong to the age ranging from 20-50 years in the Rabeprazole group.

Around 63% of the study participants belong to the age ranging from 20-50yrs in the Esomeprazole group (table 1). The two treatment groups were balanced for these demographic and baseline characteristics.

Efficacy Evaluation:

Mean percentage of 6point scale at week 0, 4 & 8 were shown in table 2. Around 90% of the study population have moderate to severe or severe and intolerable score in rabeprazole group. Around 93% of the study population have moderate to severe or intolerable score in esomeprazole group. At visit 1, 6point scale score is reduced in rabeprazole group compared to esomeprazole group (Table 2) and the result is statistically significant. At visit 2, 6point scale score is reduced in rabeprazole group compared to esomeprazole group (Table 2, Chart 1& 2) and the result is statistically significant.The reduction of symptoms score is better in Rabeprazole group compared to Esomeprazole group (Table 3)**.** Mean reduction of symptom score at 4^{th} week and 8^{th} week compared to the start is better in Rabeprazole group compared to Esomeprazole group [2.57 vs 1.87 and 3.93 vs 3.6] respectively, and the difference are statistically significant (Table 4). Table 5 shows that around 60% of the study subjects are grade 3 and 40% of study subjects were grade 4 in Rabeprazole group.Around 60% of the study subjects were grade 4 and 40% of study subjects were grade 3 in Esomeprazole group. Above 90% of study subjects have normal endoscopic findings after eight weeks of drug therapy. Only 63% of the study population have normal endoscopic findings while the rest had findings reduced to grade 1 or grade 2 and the result is statistically significant. (Table 6) 93.3 % of the study population who had grade 3 or 4 became normal after 8 weeks of drug therapy in Rabeprazole group. Endoscopic findings at the start of the study and after eight weeks are statistically significant. In Esomeprazole group, only 83.3 % of the study population who had grade 3 or 4 became normal after 8 weeks of drug therapy in Esomeprazole group.

SAFETY EVALUATION

Both treatment regimens are well tolerated during the study. After 8 weeks of study. More patients reported adverse events in Esomeprazole group than in Rabeprazole group (Table 7). In patients who had adverse reactions, 92 % of the study subjects became free of symptoms after the drug therapy in Rabeprazole group and only 69 % of the study subjects became free of symptoms after the drug therapy in Esomeprazole group. Major Complaints are Nausea and Headache in both the groups. The adverse events are only mild or moderate in intensity, hence no patients withdrew from the study.

TABLE : 1

DISTRIBUTION OF STUDY POPULATION ACCORDING TO SEX & AGE

	RABEPRAZOLE	**ESOMEPRAZOLE**
MALE	15(50)	17(56.7)
FEMALE	15(50)	13(43.3)
AGE		
<20	2(6.7)	0
20-30	7(23.3)	11(36.7)
30-40	8(26.7)	4(13.3)
40-50	7(23.3)	4(13.3)
50-60	5(16.7)	7(23.4)
60-70	1(3.3)	4(13.3)
>70	0	0

TABLE: 2

DISTRIBUTION OF SYMPTOMS BEFORE THE START,
AT 4 WEEKS AND 8 WEEKS OF DRUG THERAPY IN BOTH THE GROUPS

SYMPTOM SCORE	**RABEPRAZOLE**			**ESOMEPRAZOLE**		
	0 week	**4weeks**	**8weeks**	**0 week**	**4weeks**	**8weeks**
NONE	0	0	17(56.7)	0	0	10(33.3)
MILD	0	5(16.7)	11(36.7)	0	0	15(50)
MODERATE	3(10)	24(80.0)	2(6.6)	2(6.7)	14(46.7)	5(16.7)
MODERATE – SEVERE	11(36.7)	1(3.3)	0	13(43.3)	15(50)	0
SEVERE AND INTOLERABLE	16(53.3)	0	0	15(50)	1(3.3)	0

TABLE 3:

COMPARISON OF SYMPTOM SCORE AT THE START, AT 4 AND 8 WEEKS

SYMPTOM SCORE	RABEPRAZOLE	ESOMEPRAZOLE
	MEAN± SD	MEAN± SD
AT START	4.43±0.679	4.43±0.626
AT 4 WEEKS	1.87±0.434	2.57±0.568
AT 8 WEEKS	0.5±0.630	0.83±0.699

Chart 1: DISTRIBUTION OF SYMPTOMS BEFORE THE START, AT 4 WEEKS AND 8 WEEKS OF DRUG THERAPY IN RABEPRAZOLE GROUPS

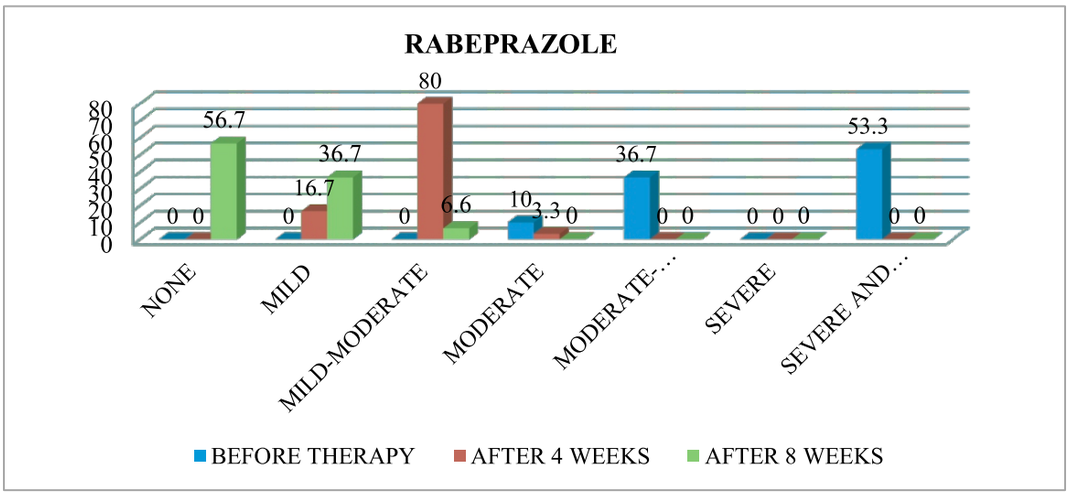

Chart 2: DISTRIBUTION OF SYMPTOMS BEFORE THE START, AT 4 WEEKS AND 8 WEEKS OF DRUG THERAPY IN ESOMEPRAZOLE GROUPS

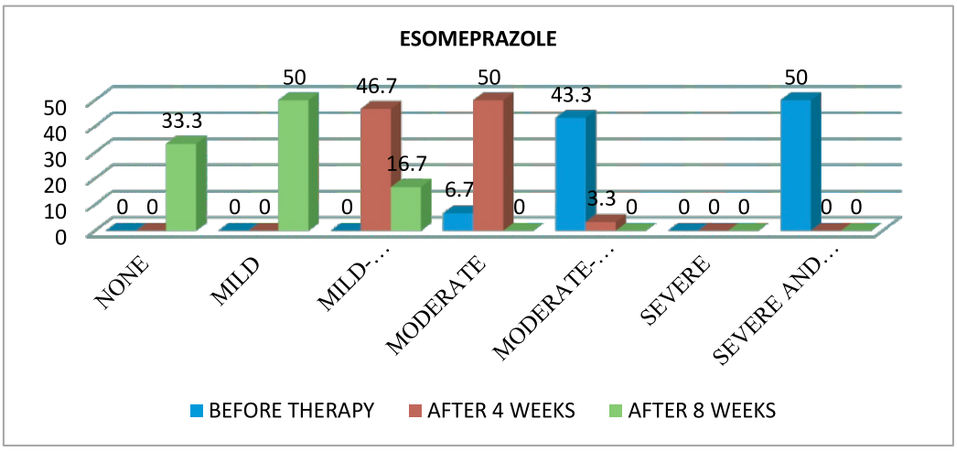

TABLE : 4 COMPARISON OF MEAN AND STANDARD DEVIATION BETWEEN SYMPTOM SCORE AT DIFFERENT PERIODS

SCORE	**RABEPRAZOLE**			***ESOMEPRAZOLE***		
	MEAN DIFFERENCE	SD	p value	MEAN DIFFERENCE	SD	P Value
START VS 4WEEKS	2.567	0.626	0.001	1.867	0.507	0.001
START VS 8WEEKS	3.933	0.828	0.002	3.600	0.724	0.002
4WEEKS VS 8WEEKS	1.367	0.718	0.004	1.733	0.640	0.004

TABLE : 5 ENDOSCOPIC FINDINGS IN BOTH THE GROUPS BEFORE THE START OF THE STUDY, AT 4 AND 8 WEEKS

ENDOSCOPIC FINDING	**RABEPRAZOLE**		***ESOMEPRAZOLE***	
	Start	**8 Weeks**	**Start**	**8 Weeks**
GRADE 1	0	2(6.7)	0	5(16.7)
GRADE 2	0	0	0	6(20)
GRADE 3	18(60)	0	12(40)	40
GRADE 4	12(40)	0	18(60)	60
GRADE 5	0	0	0	0
NORMAL		28(93.3)		19(63.3)

TABLE: 6 ASSOCIATION BETWEEN ENDOSCOPIC FINDINGS AT THE START OF THE STUDY WITH THE FINDINGS AFTER EIGHT WEEKS OF RABEPRAZOLE & ESOPMEPRAZOLE

	RABEPRAZOLE			ESOPMEPRAZOLE		
	GRADE1	**NORMAL**	**P-VALUE**	**GRADE1**	**NORMAL**	**P-VALUE**
GRADE 3	0	18(93.3%)	0.046	0	12(83.3%)	0.073
GRADE 4	2	10		5	13	

TABLE : 7 ADVERSE REACTIONS AFTER FOUR WEEKS OF DRUG THERAPY

ADVERSE REACTIONS FREQUENCY(%)	**RABEPRAZOLE**		**ESOMEPRAZOLE**	
	4weeks	**8weeks**	**4weeks**	**8weeks**
NO SYMPTOMS	17(56.7)	29((96.7)	17(56.7)	
NAUSEA	3(10)		5(16.7)	1(3.3)
HEADACHE	4(13.3)	1(3.3)	2(6.7)	2(6.7)
CONSTIPATION	2(6.7)		2(6.7)	1(3.3)
ABDOMINAL PAIN	1(3.3)			
NAUSEA + CONSTIPATION	2(6.7)		1(3.3)	
NAUSEA + HEADACHE	2(6.7)		2(6.7)	
HEADACHE + CONSTIPATION	1(3.3)		1(3.3)	

DISCUSSION

The goal of treatment of GERD is to provide rapid relief of symptoms and reducing the severity and it is measured by 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. Symptom score present in our study, are in comparison with other study by Rituparnamaiti et al., conducted trial on efficacy and safety of abeprazole and Esomeprazole in mild to moderate GERD. 30 patients receiving Rabeprazole 40mg 30 patients receiving Esomeprazole 40mg for 4 weeks. Symptoms were reduced in Rabeprazole group(34.3%) compared with Esomeprazole group(23%)[20]. The other study done by KM Fock et al., a randomized double blind study in urban Asia Rabeprazole versus Esomeprazole in non – erosive gastroesophageal reflux disease.67 patients receiving Rabeprazole 10mg and 67 patients receiving Esomeprazole

20mg for 4weeks.There was no statistically significant difference between two groups for day and night time symptom score was achieved in 98% of patients receiving Rabeprazole and 81.4% of patients receiving Esomeprazole[4].

Esomeprazole was comparable to omeprazole, lanzoprazole, pantoprazole for symptom relief in patients with reflux esophagitis by Ri-nan zheng. The present study showed that the symptom score was reduced in Esomeprazole group compared with other drugs but no significant in acid reflux score was seen between groups[12].The mean symptom scores of heartburn and acid reflux in all patients with both drugs were assessed at start, at 4 weeks and at 8 weeks shown in table 6. The mean scores were reduced in Rabeprazole group (0.5) compared to Esomeprazole group (0.83). This result is compared by with study Ri-Nan Zheng, the Mean score was reduced in Esomeprazole group than other PPI[12]. The endoscopic findings in our study shows that 93.3% of the study population who had grade 3 or 4 became normal after 8 weeks of drug therapy in Rabeprazole group whereas in Esomeprazole group only 83.3% of the study population who had grade 3 or 4 became normal after 8 weeks of drug therapy. Incidence of residual esophagitis after 8 weeks were higher in Esomeprazole group compared to Rabeprazole group. The endoscopic findings present in our study are in comparison with other study by Rituparnamaiti et al., the endoscopic findings showed that the incidence of residual esophagitis after 4 weeks was higher in Esomeprazole group compared to the Rabeprazole group[20].

Ri-nan zheng conducted trial on reflux esophagitis there was no significance differences between the four groups in the rate of endoscopic healing of GERD at week 8[12]. Altay celebi et al., conducted trial on comparison of the effect of Esomeprazole 40mg, Rabeprazole20mg, lansoprazole 30mg, and pantoprazole 40mg on intragastric PH in extensive metabolizer patients with gastroesophageal reflux disease, there were no statistical significance between Esomeprazole and Rabeprazole in acid suppression[21]. Several mechanism may explain the superior efficacy of Rabeprazole in increasing the intragastric PH and decreasing the acid output. Rabeprazole has the highest PKa of all PPIs[10]. Rabeprazole have more prolonged and potent acid inhibitory effects due to continued binding to proton pump transmembrane domains even after achieving 100% of inhibition of the ATPase activity[11]. In extremely acidic environments PPIs may have similar equipotency[22]. In less acidic environments Rabeprazole given its rapid activation over wide PH range and targets a greater population of parietal cells to give more rapid and pronounced degree of acid inhibition. In older parietal cells Rabeprazole can be as much as 10 times more potent than other PPIs[22]. The superiority of Rabeprazole over Esomeprazole found in our study because of increasing intragastric PH and maintaining PH > 3 & PH > 4. In our study both Rabeprazole and Esomeprazole were well tolerated without any severe side effects. The present study supports the finding of previous study by Fock et al., and pai et al., shows that there was no significant difference in adverse drug reaction between the groups. Like other PPI Rabeprazole and Esomeprazole were well tolerated without any severe side effects

CONCLUSION

On the basis of present clinical comparative study, it can be concluded that the Rabeprazole 20mg OD daily is more effective than Esomeprazole 40mg OD daily for the treatment of mild to moderate GERD. The incidence of residual esophagitis after 8 weeks were lower in Rabeprazole group and the symptom score was reduced in Rabeprazole group. Apart from this coast effectiveness is high in Rabeprazole. Hence our study suggests that Rabeprazole may have superior efficacy in mild to moderate GERD.

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