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# The effect of rabeprazole alone or in combination with $H_2$ receptor blocker on intragastric pH: A pilot study

## Rabeprazol'un tek başına veya $H_2$ reseptör ile kombine kullanımının intrahepatik pH üzerine etkisi: Pilot çalışma

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***Background/aims:*** *Proton pump inhibitors have been widely used in recent years. However, there are studies suggesting that proton pump inhibitors may not control the gastric acidity effectively during the night, especially in gastroesophageal reflux disease. It has therefore been suggested that $H_2$ receptor blockers should be added to the therapy. The aim of our study was to evaluate the effects of proton pump inhibitors alone or in combination with $H_2$ receptor blockers on gastric acidity with 24-hour gastric pH monitoring.* ***Methods:*** *Esophagogastroscopy and 24-hour gastric pH monitoring were performed on 10 patients with dyspeptic symptoms. No patient had anacidity. All patients had erosive antral gastritis. Patients were randomized to two groups as either proton pump inhibitor therapy group (rabeprazole 20 mg/day, p.o.) or proton pump inhibitor + $H_2$ receptor blocker therapy group (rabeprazole 20 mg/day, p.o. + famotidine 40 mg/day, p.o). After one month of treatment, 24-hour gastric pH monitoring was re-performed.* ***Results:*** *Seven female and three male patients were enrolled into the study. The mean age was 51.1±11.56 years. All patients had antral erosive gastritis. Gastric pH was measured as less than 4 in 81.4% of the 24-hour period prior to rabeprazole treatment. With rabeprazole treatment this ratio decreased to 27.6% ($p<0.05$). These ratios were 86.3% and 4.55%, respectively, in the group that received combination therapy ($p<0.05$).* ***Conclusions:*** *Combination therapy with $H_2$ receptor blockers and proton pump inhibitors seemed to control intra-gastric pH better than proton pump inhibitors alone. Use of $H_2$ receptor blockers and proton pump inhibitors in combination to control intra-gastric pH is more beneficial.*

Key words: Rabeprazole, $H_2$ receptor antagonist, intragastric pH

***Amaç:*** *Proton pompa inhibitörlerinin kullanımı son yıllarda giderek artmaktadır. Ancak özellikle gastroözofajiyal hastalarında proton pompa inhibitörü kullanımının gece tam olarak gastrik asiditeyi kontrol etmediği ve bu yüzden tedaviye $H_2$ reseptör blokerlerinin eklenmesi gerektiği savunulmaktadır. 24 Saatlik gastrik pH monitorizasyonu ile proton pompa inhibitörü kullanımı ve proton pompa inhibitörü + $H_2$ reseptör blokeri kullanımının gastrik asidite üzerine etkilerini karşılaştırmaktır.* ***Yöntem:*** *Çalışmaya dispeptik semptomlarla başvuran 10 hasta dahil edildi. Bu hastaların hepsine üst gastrointestinal sistem endoskopisi yapılldıktan sonra, 24 saatlik gastrik pH monitorizasyonu uygulandı. Hastaların hiç birisinde anasidite mevcut değildi. Hastalar 2 gruba ayrıldıktan sonra bir gruba sadece proton pompa inhibitörü (Rabeprozol 20 mg/gün, po), diğer gruba ise proton pompa inhibitörü + $H_2$ reseptör blokeri (Rabeprozol 20 mg/gün p.o.+ Famotidin 40 mg/gün p.o.) 1 ay süre ile tatbik edildi. 1 ay sonunda 24 saatlik gastrik pH monitorizasyonu tekrarlandı.* ***Bulgular:*** *Çalışmaya 7 bayan, 3 erkek hasta alındı. Hastaların ortalama yaşı 51.1±11.56 yıl idi. Çalışmaya alınan hastaların hepsinde eroziv antral gastrit mevcut idi. Proton pompa inhibitörü verilen grupta tedavi öncesi gastik pH'nın <4 olduğu zaman %81.4 iken tedavi sonrası bu oran %86.3 iken tedavi sonrası bu oran %4.55'e düştü ($p<0.05$).* ***Sonuç:*** *Proton pompa inhibitörleri ile $H_2$ reseptör blokerlerinin kombinasyonu gastrik asidiyeti tek başına proton pompa inhibitörü tedavisine oranla daha belirgin olarak kontrol etmektedir. intragastrik asidite supresyonunda proton pompa inhibitörü $H_2$ reseptör blokerlerinin kombine kullanılması daha faydalı olacaktır.*

Anahtar kelimeler: Rabeprozol, $H_2$ reseptör antagonisti, intragastrik pH

## INTRODUCTION

Diseases related to gastric acidity were treated with $H_2$ receptor blockers and antiacids up to the 1990's, after which time, proton pump inhibitors have been widely used in peptic ulcer disease, gastroesophageal reflux disease (GERD) and Zollinger-Ellison syndrome. The first proton pump inhibitor used in clinical trials was omeprazole (1), which was shown to have more gastric acid inhibi-

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ting effect than all chemotherapeutics at that time. The healing time for peptic ulcers was shortened, the remission time in GERD extended, and the successful healing of peptic esophagitis increased with the use of omeprazole. In addition, it has been observed that these agents suppress *Helicobacter pylori* infection and may also potent the antibiotic action in peptic ulcer disease (2). These positive effects have led to the introduction on the market of various proton pump inhibitors with different pharmacodynamic properties: lansaprazole (3), pantaprazole (4), rabeprazole (5), tenatoprazole (6), and esomeprazole (7).

In spite of these favorable effects of proton pump inhibitors, 15-30% of patients with GERD have ongoing symptoms and esophageal lesions that do not heal. One of the reasons for the resistance to the proton pump inhibitors is because of the insufficient suppression of the nocturnal gastric acidity. This phenomenon is known as "nocturnal acid breakthrough". The most common method used today to overcome this complication is the addition of an $H_2$ receptor blocker to the proton pump inhibitor therapy (9, 10).

The aim of our study was to evaluate the effect of a proton pump inhibitor, rabeprazole, alone or in combination with a $H_2$ receptor blocker on intragastric pH control and nocturnal acid breakthrough phenomenon.

## MATERIALS AND METHODS

Patients with dyspeptic symptoms admitting to the Ankara University Medical Faculty Gastroenterology Department outpatient clinic were evaluated for the following inclusion criteria of the study:

1. Dyspeptic symptoms
2. No history of any anti-inflammatory drug usage
3. No history of a proton pump inhibitor usage (for at least 8 weeks before study)
4. No history of a $H_2$ receptor blocker usage (for at least 1 week before study)
5. Erosive gastritis on gastroesophagoscopy
6. No duodenal ulcer or endoscopic esophagitis on gastroesophagoscopy
7. No history of total/partial gastrectomy or sur gery for duodenal ulcer
8. Negative urease test for *Helicobacter pylori*

Ten patients who fulfilled the above criteria were included in the study. Upper gastrointestinal endoscopy and 24-hour gastric pH monitoring were performed on the patients.

The patients were then randomized to two groups as either the proton pump inhibitor therapy group (rabeprazole 20 mg/day, p.o.) or the proton pump inhibitor + $H_2$ receptor blocker therapy group (rabeprazole 20 mg/day, p.o. + famotidine 40 mg/day, p.o.). It was recommended to the patients that rabeprazole be taken half an hour prior to breakfast and that famotidine be taken before going to bed at night. After one month of treatment, 24-hour gastric pH monitoring was performed again. In 24-h gastric pH monitoring, the percentage of time that intra-gastric pH was recorded as less than 4 was calculated, the presence of nocturnal acid breakthrough was evaluated, and these parameters were compared in the two groups.

SPSS 10.0 for Windows program was used for statistical analysis. Descriptive statistics and Student's t-test were used. A p value $< 0.05$ was considered as statistically significant.

## RESULTS

Ten patients (3 men, 7 women) were included in the study. The mean age±SD was 51.1+15.6 (22-73) years. All patients had erosive gastritis on esophagogastroscopy. No adverse events were observed during therapy and there were no complications in 24-h intragastric pH monitoring.

Before the therapy, pH was <4 for 83.5±5.9% of the time with 24-h intragastric pH measurements. In the rabeprazole group, pH was <4 for 81.4% of the time in 24-h intragastric pH measurements before therapy. However, this time reduced to 27.6% after one month of therapy ($p<0.004$). In the rabeprazole + famotidine group, pH was <4 for 86.3% of the 24-h period before therapy, whereas it was reduced to 4.5% after one month of therapy ($p<0.0001$), as shown in (Figure 1). The gastric acid suppression was significantly greater in the rabeprazole + famotidine group compared to the group receiving rabeprazole alone; however, this difference was more obvious during the night.

## DISCUSSION

We obtained better gastric acid suppression with rabeprazole + famotidine than with rabeprazole therapy alone, especially during the night, in our study. Acidity suppression during the day did not differ between the treatment groups.

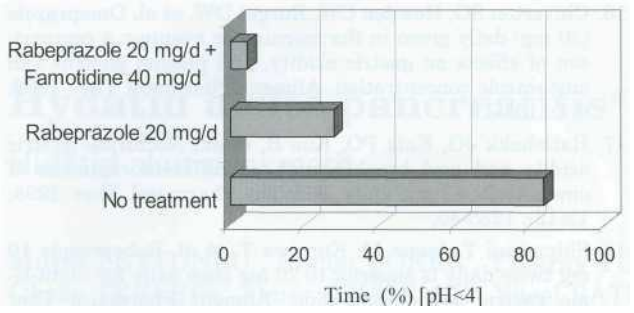


**Figure 1.** The effects of treatment on 24 hr intragastric pH measurements

In some studies it has been shown that *Helicobacter pylori* infection may alter the antisecretory effects of proton pump inhibitors (11, 12). For this reason, patients with *Helicobacter pylori* infection were not included in this study.

Studies have revealed that rabeprazole was more effective in controlling the nocturnal acid breakthrough than lansaprazole and omeprazole (13, 14). Pehlivanov et al. (15) compared morning and evening administration of rabeprazole in reflux disease. When taken in the morning, rabeprazole was found to decrease the time pH was <4 in supine position from 88.7% to 52.1%, and in upright position from 87.9% to 39.7%. Similar results were obtained when rabeprazole was taken in the evening. However, the esophagus had already been exposed to the acidity in the supine position when rabeprazole was administered in the evening.

Chiverton et al. (16) suggested that omeprazole's gastric acid suppression was optimum when administered in the morning at a dosage of 20 mg. In another study; however, it was reported that gastric acid suppression was improved when omeprazole was given in two divided doses versus once a day (17). In another study, lansaprazole (30 mg) and omeprazole (20 mg) were administered twice daily and nocturnal acid breakthrough was observed in both treatment groups (8). We have also shown in this study that rabeprazole alone was not effective in controlling gastric acidity. In a recent study, rabeprazole (20 mg/once a day) and rabeprazole (10 mg twice a day) administrations were compared. Intragastric pH was >4 for 52% of the 24-h period when taken once a day, and for 85% when taken twice daily (18). In our study these values were 73.4% with rabeprazole and 95.45% with rabeprazole + $H_2$ receptor blocker. Therefore, we can speculate that use of $H_2$ receptor blockers and proton pump inhibitors in combination may control intra-gastric pH better than proton pump inhibitors alone, even if they are used twice a day.

In summary, proton pump inhibitors alone are not adequate in controlling gastric acid suppression, although long-acting proton pump inhibitors like rabeprazole do demonstrate better gastric acidity control in divided doses. We suggest that adding an $H_2$ receptor blocker to a proton pump inhibitor is a better choice for treatment, as the combination is more effective for the control of 24-h gastric acidity.

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