PPIs in Gastric Acid–Related Diseases

During the past two decades, enormous changes occurred in the management of gastric acid–related diseases. First, the histamine₂–receptor antagonists were introduced, offering patients the first single–agent therapy that effectively reduced gastric acid secretion. Since the introduction of PPIs, most physicians now use them as first–line treatment for patients with acid–peptic disorders, including erosive gastro–oesophageal reflux disease (GERD), nonerosive reflux disease (NERD) and duodenal and gastric ulcers.¹

Proton pump inhibitors (PPIs) act selectively on the final stage of the process of gastric acid secretion, namely the H⁺/K⁺ –ATPase or proton pump. This enzyme represents an essential step in the process of secretion of H⁺, and PPIs exert a very specific action on the parietal cell, as they need an environment with very low pH levels, which only exist in this cell. After two decades of use, PPIs have proved to be very effective and safe drugs. The significant inhibitory capacity of gastric acid secretion of PPIs makes them the drugs of choice for treating acid–related diseases.²

Metabolism and Efficacy of PPIs: Focus on Rabeprazole

Although all proton pump inhibitors are highly effective, the antisecretary effects of different drugs in this class are not completely consistent across patients. An important reason for interpatient variability of the effects of proton pump inhibitors on acid secretion involves genetically determined differences in the metabolism of these drugs.

Results reviewed indicate that the metabolism and pharmacoki–

Advantages of Sodium Bicarbonate Buffer

- Although PPIs are stable at alkaline pH, they are destroyed rapidly as pH falls (e.g., by gastric acid). Therefore, if the micro-encapsulation or the enteric coating is disrupted (e.g., trituration to compound a liquid, or chewing the capsule), the dosage forms of the prior PPIs will be exposed to degradation by the gastric acid in the stomach. Hence, previously all oral PPIs were delayed-release, enteric-coated formulations designed to prevent degradation of the drug by gastric acid.
- The enteric dosage forms of the prior PPIs were employed because they are acid labile; thus, it is important that these drugs not be exposed to low pH gastric acid prior to absorption. Unfortunately, enteric coatings delay absorption and initial acid suppression.
- RABIFINE FR tablets contains sodium bicarbonate, which protects the drug from gastric acid degradation. This provides the benefits of the proton pump inhibitor without the drawbacks of the current enteric-coated solid dosage forms.
- Moreover, this built–in sodium bicarbonate buffer protects RABIFINE FR from acid degradation by raising intragastric pH. No enteric coating of capsules or powder for oral suspensions are thus required. In this form, the drug is faster acting and may also be useful for patients who are unable to swallow and have nasogastric (NG) tubes in place.³
Pharmacokinetics of rabeprazole differ significantly from those of other proton pump inhibitors. Most importantly, the clearance of rabeprazole is largely non-enzymatic and less dependent on CYP2C19 than other drugs in its class. This results in greater consistency of pharmacokinetics for rabeprazole across a wide range of patients with acid-related disease, particularly those with different CYP2C19 genotypes.

The pharmacodynamic profile for rabeprazole is also characterized by more rapid suppression of gastric acid secretion than with other proton pump inhibitors, which is also independent of CYP2C19 genotype. The favorable pharmacokinetic/pharmacodynamic profile for rabeprazole has been shown to result in high eradication rates for *H. pylori* and duodenal and gastric ulcer. Treatment efficacy has been strongly correlated with degree and duration of acid suppression within the 24-h period and with total duration of therapy.

All PPIs have closely similar mechanisms of action, yet important pharmacological differences exist, which can significantly impact certain aspects of their clinical efficacy. Rabeprazole’s has an early onset of effective acid inhibition compared with other proton pump inhibitors such as omeprazole, lansoprazole and pantoprazole. Like rabeprazole, esomeprazole is also a potent inhibitor of gastric acid at steady state, although it is thought that rabeprazole may provide enhanced first-day acid suppression compared with esomeprazole.

First-day antisecretory efficacy should produce faster symptom relief, a hypothesis supported by clinical data. Moreover, drugs with pharmacological profiles that include both rapid onset and potent antisecretory effects should help control healthcare costs by reducing the need for otherwise commonly used twice-daily proton pump inhibitor administration. Rabeprazole which has been further enhanced with sodium bicarbonate buffer provides even better results.

**ROLE OF RABEPROAZOLE TREATMENT IN ACID-RELATED DISORDERS**

Control of gastric acid secretion by antisecretory agents has been the cornerstone of therapy in the successful management of all acid-related disorders, including gastro-oesophageal reflux disease (GERD), and duodenal and gastric ulcer. Treatment efficacy has been strongly correlated with degree and duration of acid suppression within the 24-h period and with total duration of therapy.

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**ACID INHIBITION ON THE FIRST DAY OF DOSING: COMPARISON OF FOUR PPIs**

To compare the antisecretory activity and onset of action of single doses of rabeprazole, lansoprazole, pantoprazole, omeprazole capsule, omeprazole multiple unit pellet system (MUPS) tablet and placebo in healthy *Helicobacter pylori*-negative subjects, this cross-over, double-blind, randomized study was performed in 18 *H. pylori*-negative subjects.

The intragastric pH (3.4) and time at pH > 4 during the 24 h post-dose (8.0 h) were significantly greater with rabeprazole than with lansoprazole, pantoprazole, omeprazole capsule, omeprazole MUPS tablet or placebo (P ≤ 0.04 for rabeprazole vs. the others). Daytime and night-time pH values were higher with rabeprazole and lansoprazole than with pantoprazole, omeprazole capsule and omeprazole MUPS tablet (P ≤ 0.04). Rabeprazole was the most potent acid inhibitor of all the proton pump inhibitors tested during the first day of dosing. Rabeprazole which has been further enhanced with sodium bicarbonate buffer will provides even better results because of raised pH.

**ERADICATION OF H. PYLORI**

Eligible patients with persistent infection following one or more conventional clarithromycin-containing triple therapies were enrolled in this open-label trial. A total of 45 patients (22 females: 23 males; mean age 44.5 ± 13 years) were enrolled. Eradication occurred in 38 patients [both per-protocol (PP) and intention-to-treat analysis: 84.4%; 95% CI: 74–95%]. No significant adverse effects were reported. In vitro susceptibility testing showed no secondary resistance to gatifloxacin or amoxicillin in any of the seven non responders. A 7-day regimen of gatifloxacin, rabeprazole, and amoxicillin is effective after failed eradication therapy for *H. pylori* and does not appear to result in secondary resistance. This combination is simple, well tolerated, and may lead to higher compliance and lower costs.

**COMPARISON OF FOUR PPIs FOR THE TREATMENT OF ESOPHAGITIS**

A total of 320 patients over 65 years with endoscopically diagnosed esophagitis were randomly assigned to one of the following treatments for 8 wks: (1) omeprazole 20 mg/d; (2) lansoprazole 30 mg/d; (3) pantoprazole 40 mg/d, or (4) rabeprazole 20 mg/d. Major symptoms, compliance, and adverse events were recorded. After 8 wks, endoscopy and clinical evaluation were repeated.

Per protocol and intention to treat healing rates of esophagitis were: omeprazole = 81.0% and 75.0%, lansoprazole = 90.7% (P = 0.143 vs omeprazole) and 85.0%, pantoprazole = 93.5% (P = 0.04 vs omeprazole) and 90.0% (P = 0.02 vs omeprazole), rabeprazole = 94.6% (P = 0.02 vs omeprazole) and 88.8% (P = 0.04 vs omeprazole). Dividing patients according to the grades of esophagitis, omeprazole was significantly less effective than the three other PPIs in healing grade 1 esophagitis (healing rates: 81.8% vs 100%, 100% and 100%, respectively, P = 0.012).

Pantoprazole and rabeprazole (100%) were more effective vs omeprazole (90.6%, P = 0.0001) and lansoprazole (82.4%, P = 0.0001) in decreasing heartburn. Pantoprazole and rabeprazole (92.2% and 90.1%, respectively) were also more effective vs lansoprazole (75.0%, P < 0.05) in decreasing acid regurgitation. Finally, pantoprazole and rabeprazole (95.2% and 100%) were also more effective vs lansoprazole (82.6%, P < 0.05) in decreasing epigastric pain.

In elderly patients, pantoprazole and rabeprazole were significantly more effective than omeprazole in healing esophagitis and than omeprazole or lansoprazole in improving symptoms. *H. pylori*...
infection did not influence the healing rates of esophagitis after a short–term treatment with PPI. Rabeprazole which has been further enhanced with sodium bicarbonate buffer will provides even better results.

**ORAL RABEPRAZOLE VS. INTRAVENOUS PANTOPRAZOLE**

Intravenous pantoprazole is often administered inappropriately to hospitalized patients who can take oral medications. In a double–blind, double–dummy, two–way crossover study, 38 *H. pylori*–negative volunteers were randomized to oral rabeprazole 20 mg or intravenous pantoprazole 40 mg daily for 3 days followed, after a 14–day washout period by the comparator treatment.

The mean (95% CI) percentage of the 24–h recording with gastric pH >4 was higher with rabeprazole than with pantoprazole on day 1: 37.7% (30.6–44.8%) vs. 23.9% (20.0–27.8). The mean percentage times with pH >3 and >4 for all intervals assessed were greater and the median 24–h intragastric pH values were higher with rabeprazole than with pantoprazole on days 1 and 3. The mean acidity index was lower with rabeprazole on days 1 and 3.

In conclusion, oral rabeprazole 20 mg produced greater acid suppression than intravenous pantoprazole 40 mg. Therefore, it may be an appropriate and effective alternative in patients who can take oral medication. Rabeprazole which has been further enhanced with sodium bicarbonate buffer gives even better results.

**HIGHLIGHTS**

- Sodium bicarbonate added as a buffer to rabeprazole provides prolonged yet immediate effect because it prevents rabeprazole from acid degradation by raising pH due to which tablets are not enteric coated
- In 8-week studies, among patients with gastro-esophageal reflux disease (GERD), rabeprazole 20 mg/day or 10 mg twice daily was as effective as omeprazole and superior to ranitidine in the healing of GERD. Symptom relief with rabeprazole was superior to that provided by placebo and ranitidine and similar to omeprazole
- In long-term trials rabeprazole 10 mg/day was similar to omeprazole 20 mg/day in a 2-year study and superior to placebo in 1-year studies, in both the maintenance of healing and prevention of symptoms in patients with healed GERD
- In nonerosive GERD, 4-week studies have shown rabeprazole to be more effective than placebo in relieving heartburn and various other gastrointestinal symptoms
- Data among patients with Barrett’s oesophagus suggest rabeprazole 20 mg/day may be more effective than placebo in maintaining healing of associated oesophagitis after 1 year of treatment.
- As monotherapy for peptic ulcer healing and symptom relief, 4- to 8-week studies have shown rabeprazole 10 to 40 mg/day to be superior to placebo and ranitidine and have similar efficacy to omeprazole
- Preliminary 1-year data among 16 patients with Zollinger–Ellison syndrome suggest rabeprazole 60 to 120 mg/day can resolve and prevent the recurrence of symptoms and endoscopic lesions associated with this condition.

**REFERENCES**

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