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Review

# Potential Implementation of Rabeprazole in Prevention of Acidity in GIT: Updated Mini-Review

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***Abstract:***

*Rabeprazole is a proton pump inhibitor. Pharmacodynamics data show rabeprazole can achieve optimal acid suppression since the first administration and can maintain this advantage in the following days of therapy. Moreover, rabeprazole has the highest pKa (~ 5.0, the pH at which a drug becomes 50% protonated), and hence the molecule can be activated at higher pH levels much faster than other PPIs. Due to its peculiar catabolic pathway, ie, a prevalent metabolism through a non-enzymatic pathway, rabeprazole is less susceptible to the influence of genetic polymorphisms for CYP2C19, resulting in minor influences on its pharmacokinetics and pharmacodynamics. To prevent symptomatic relapse, on-demand strategy with rabeprazole 10 mg daily appears to be ideal, due to its rapidity of onset; results on NERD patients have documented its superiority over placebo. Continuous treatment, however, up to 5 years, seems to achieve better results than on-demand therapy, particularly in patients with esophagitis.*

***Keywords:*** *Proton pump inhibitor, Gastric acid, Rabeprazole GERD.*

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## Introduction

The most effective way to increase the pH in the stomach, and hence to reach a therapeutic level for GERD, is the blockage of the proton pump enzymes in the parietal cells. All PPIs, being substituted benzimidazoles, share the same anti-secretory mechanism: to be activated, they concentrate in the secretory canaliculus of the parietal cell thanks to the acid milieu of the environment. The protonated molecules undergo a conversion to an active sulfenamide compound (the rate-limiting step) and, in this state, form covalent inhibiting disulfi de bonds with surface-exposed cysteines of the active parietal cell H+/K+-ATPase. In an isolated hog vesicle model, rabeprazole confirmed its potent and fast onset of action: within 5 min of rabeprazole exposure the proton pump was near-maximally inhibited. The same target was reached after 30 min for lansoprazole and omeprazole; but pantoprazole could only inhibit the 50% of the pump by the end of the 50 minute test (Besancon et al 1997). Therefore, rabeprazole sodium produces a dose-related sustained inhibition of both basal and peptone meal-stimulated gastric acid secretion (Lew et al 1998; Ohning et al 2003).

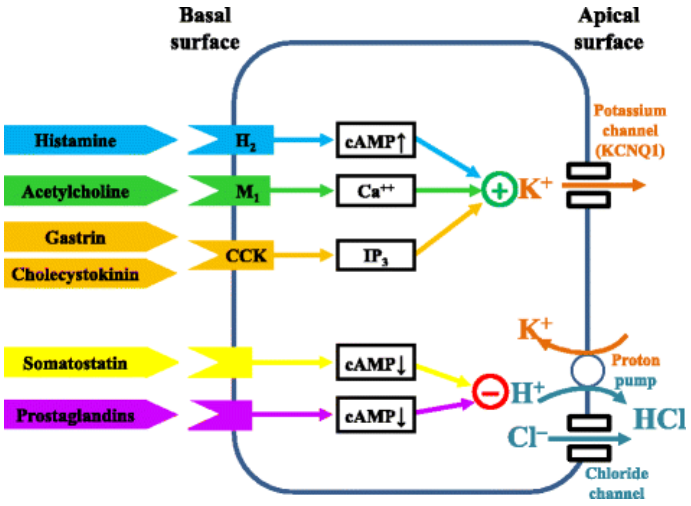



**Fig 1:** A simplified description of the physiology of gastric acid secretion; other compounds involved in its regulation, not shown, include ghrelin, glutamate, pituitary adenylase cyclase-activating peptide (PACAP), and serotonin (5HT).

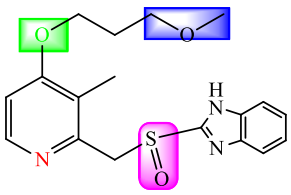
It is widely recognized that the anti-secretory activity of PPIs is predictive of their efficacy in acid-related disorders. It has been shown that duodenal ulcer healing correlates with an intra gastric pH >3 holding time of 18–20 hours, while erosive GERD healing with about a round-the-clock pH >4 holding time (Burget et al 1990; Bell et al 1992).

A reduced dose of rabeprazole (10 mg od) exhibited better antisecretory activity than either omeprazole 20 mg od or lansoprazole 30 mg od in a study that analyzed the percentage of time pH 3 on each of the fi rst three days of therapy in 8 H. pylori-negative CYP2C19 extensive metabolizers. On days 1, 2, and 3 the ratios were 13.6%, 35.3%, and 62.8% for rabeprazole 10 mg; 7.4%, 13.6%, and 26.6% for lansoprazole 30 mg; and 6.1%, 11.4%, and 16.4% for omeprazole 20 mg (Saitoh et al 2002). Again rabeprazole 10 mg provided a faster acid inhibition compared with omeprazole 10 mg in a randomized, double-blind, placebo-controlled, three-way crossover study on 27 volunteers.

By the end of the 7-day treatment, median gastric pH was signifi cantly higher with rabeprazole than with omeprazole (3.7 vs 2.2, p = 0.0016) and the time with pH above 4 was more than doubled (10.5 vs 4.6 hours, p = 0.0008) (Bruley Des Varannes et al 2004).

A number of researchers during recent years have investigated the occurrence of nocturnal gastric acid breakthrough (NAB), which has been defi ned as the occurrence of intragastric pH dropping to below 4 for at least 1 hour during the 12 hours of night sleeping period, in GERD patients with nocturnal refl ux symptoms and have questioned whether this phenomenon is due to a failing effi cacy of PPIs over the 24 hours.

In 2003 Pehlivanov et al (2003) demonstrated that rabeprazole 20 mg, administered in the morning or in the evening, signifi cantly shortened the mean NAB duration versus the baseline recording (4.1 for rabeprazole a.m. and 3.4 for rabeprazole p.m. vs 7.8 for baseline, p < 0.05). Rabeprazole has also shown (Luo et al 2003) to be more effective than fi rst-generation PPIs in reducing the duration of NAB and, hence, increasing the nocturnal alkaline amplitude (NAKA), which has been defi ned as the occurrence of an abrupt increase in intragastric pH to above 4–6 after sleeping, mostly in the early morning. Forty patients with active peptic ulcer were randomly assigned to receive a single oral dose of rabeprazole 10 mg, omeprazole 20 mg, or pantoprazole 40 mg; the intragastric pH was monitored 1 hour before and 24 hours after the dose was given.



2-(((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methyl)sulfinyl)-1*H*-benzo[*d*]imidazole

In the rabeprazole group, the pH of NAB was statistically greater than the one in the others (1.84 vs 1.15 and 1.10 for respectively rabeprazole vs omeprazole and pantoprazole, $p < 0.01$). Rabeprazole also gave a longer time of NAKA (4.65 hours) than omeprazole (3.22 hours) and pantoprazole (3.15 hours), both $p < 0.05$ (Luo et al 2003). It must be acknowledged that in Luo's study the H. pylori status was not controlled, and this factor is known to infl uence the duration of NAB, as for example shown by the increase of NAB following H. pylori eradication (van Herwaarden et al 2000). It is possible that the newest PPIs, such as esomeprazole and the not yet marketed tenatoprazole, might be even better for control of NAB (Hunt et al 2005), although direct comparison with rabeprazole does not exist.

**Pharmacokinetics**

Rabeprazole is marketed as an enterically coated formulation, due to the instability of all PPIs in acid environment. After oral ingestion it is relatively rapidly absorbed as maximal plasma concentration (Cmax) is reached between 2.8 and 5.1 postdose (Swan et al, 1999). The pharmacokinetics of the molecule has been shown to be linear in the range 10–80 mg with an overall bioavailability of 52%, seen with rabeprazole 20 mg. Although Cmax and area under the curve (AUC) of the plasma concentration are proportional to the dose ingested, time to reach Cmax and half-life are dose-independent. This behavior confi rms that rabeprazole does not have a saturable fi rst-pass metabolism and it can be absorbed in high doses (Swan et al 1999). Neither antacids nor food infl uence the bioavailability of the molecule, even if food intake delayed the absorption of rabeprazole 20 mg of about 1.7 h and reduced the apparent elimination half-life due to a probable delayed gastric emptying (Swan et al 1999).

The impact of CYP2C19 polymorphism on pharmacokinetics of rabeprazole, omeprazole, and lansoprazole was assessed in 18 Japanese subjects (6 homozygous metabolizers, 6 heterozygous metabolizers, and 6 poor metabolizers). AUC, Cmax , and elimination half-life were not affected by CYP2C19 genotype for rabeprazole; however, AUC and Cmax were increased in poor metabolizers for lansoprazole and omeprazole (Sakai et al 2001). This predictivity of rabeprazole has the potential to reduce interpatient variability in both pharmacological and clinical effects.

Patient genetic characteristics increased the intragastric pH after single and repeated doses in heterozygous extensive and poor metabolizers versus homozygous extensive metabolizers who took omeprazole 20 mg for 8 days.

As a result of CYP2C19 polymorphism, most Caucasians (60%–70% homozygous extensive metabolizers, 28%–36% heterozygous extensive metabolizers, and 2.7%–6.1% homozygous poor metabolizers) can rapidly metabolize PPIs such as omeprazole, esomeprazole, lansoprazole, and pantoprazole and show a diminished acid inhibitory activity of these PPIs among extensive metabolizers (Furuta 2005). This phenomenon might be masked by the observation that both omeprazole and esomeprazole inhibit the activity of CYP2C19 through their sulfone metabolite and, hence, actually autoinhibit their own metabolism, resulting in a non-linear increase in blood levels of these PPIs following repeat dosing. With omeprazole 20 mg, AUC increased by 173% and with esomeprazole by 190%–265% for the 20 and 40 mg doses respectively (McColl and Kennerley 2002). The prevalent non-enzymatic metabolic pathway of rabeprazole is also the reason for the absence of drug–drug interactions between this PPI and other drugs, which are metabolized by the isoenzymes of the cytochrome P450. Co-administration of rabeprazole did not affect the pharmacokinetics of theophylline, diazepam, warfarin, and phenytoin (Thjodleifsson and Cockburn 1999). The expected interference with the pH-dependent absorption of digoxin and ketoconazole is common to all PPIs (Ishizaki and Horai 1999).

Clinical efficacy profile in GERD is a common disease affecting a large part of Western population and progressively increasing in Eastern societies. There is an ongoing debate as to whether the different manifestations of prolonged refl ux of gastric content in the esophagus should be interpreted as a disease continuum (Pace and Bianchi Porro 2004) or as different and non-communicating sub-groups (Fass and Ofman 2002). This debate is not only of theoretical relevance, because different natural courses of disease mean different expectations from the drugs we test against GERD, which in turn may affect the way we plan clinical studies. The ability to prevent the development of erosions in patients with symptoms, but without esophagitis (non-erosive refl ux disease, NERD), would be a strong endpoint for those considering GERD as a spectrum disease, while those who consider GERD an umbrella covering different non-communicating diseases would possibly not even consider the possibility of progression to erosive disease. When possible, we will consider GERD as a spectrum disease, which has milder,

non-erosive cases and longer lasting, worse, erosive or complicated cases. Data on atypical and extra-esophageal symptoms will be included as well. An extensive review covered these topics in 2023 and we will focus only on papers published after that date.

**Relapse prevention**

Studies included in this section were randomized and double-blind, and required patients to have had a previous diagnosis of erosive GERD healed within 90 days of enrolment, as demonstrated by endoscopy. At baseline endoscopy requirements included the absence of active erosions or ulcerations. The primary effi cacy endpoint in studies was the continued absence of esophageal erosions or ulcerations at follow-up endoscopic examinations. An early study compared rabeprazole with placebo (Birbara et al 2000), while a later one compared the daily dose of rabeprazole 20 mg with 10 mg and another one compared rabeprazole at the doses of 10 and 20 mg daily with omeprazole .Relapse rates after 1 year of treatment were similar (about 5%) with rabeprazole 10 or 20 mg/day and omeprazole 20 mg/day in one study, while significantly different between rabeprazole 10 and 20 mg/day (10% vs 27%; $p < 0.04$) in the other (Caos et al 2000). No significant differences between regimens were observed in secondary efficacy variables such as frequency and severity of heartburn, overall well-being, time lost from usual activities of daily living, or antacid use. These studies reported also Kaplan-Meier probabilities for remaining free of severe day-time and night-time heartburn.

**Possible new indications**

A mechanism of tumor resistance to chemotherapy may be the alteration of the tumor microenvironment via changes in the pH gradient between the extracellular environment and the cell cytoplasm (De Milito and Fais 2005), impairing the uptake of weakly basic chemotherapeutic drugs, and reducing their effect. An option to revert multi-drug resistance could be to target the vacuolar H+-ATPases (V-H+-ATPases) that pump protons across the plasma membrane. Rabeprazole directly inhibits V-H+-ATPases and PPI pretreatment sensitizes tumour cell lines to the effect of cisplatin, 5-fluorouracil and vinblastine. PPI pretreatment was associated with the inhibition of V-H+-ATPases activity and an increase of both extracellular pH and the pH of lysosomal organelles, consistent with a cytoplasmic retention of the cytotoxic drugs and targeting to the nucleus in the case of doxorubicin.

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