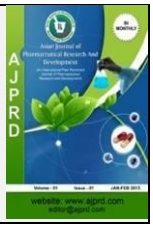
Available online on 15.10.2026 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

Potential Implementation of Rabeprazole in prevention of Acidity in GIT: Short Statement

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ABSTRACT

Rabeprazole is a proton pump inhibitor. Pharmacodynamic 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. It is debated whether in the latter halved doses (10 mg) are really equivalent to full dose (20 mg). Finally, rabeprazole achieves similar Helicobacter pylori eradication rates compared with omeprazole and pantoprazole when co-administrated with low or high doses of antibiotics (amoxicillin and clarithromycin). In addition, low doses of rabeprazole (10 mg/bid) may be effective in eradicating the pathogen.

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

ARTICLE INFO: Received 16 Feb 2026; Review Complete 25 April 2026; Accepted 27 May 2026; Available online 15 Oct. 2026

Cite this article as:

Kumar R, Gupta A, Yadav YK, Singh S, Yadav SK, Sharma M, Jain V, Kumar A, Malhotra R, Kumar P, Potential Implementation of Rabeprazole in prevention of Acidity in GIT: Short Statement, Asian Journal of Pharmaceutical Research and Development. 2026; 14(5): 154-158 DOI: **http://dx.doi.org/10.22270/ajprd.v14i5.1858**

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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 disulfide 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[1,2]. Therefore, rabeprazole sodium produces a dose-related sustained inhibition of both basal and peptone meal-stimulated gastric acid secretion [3].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 [4-6].

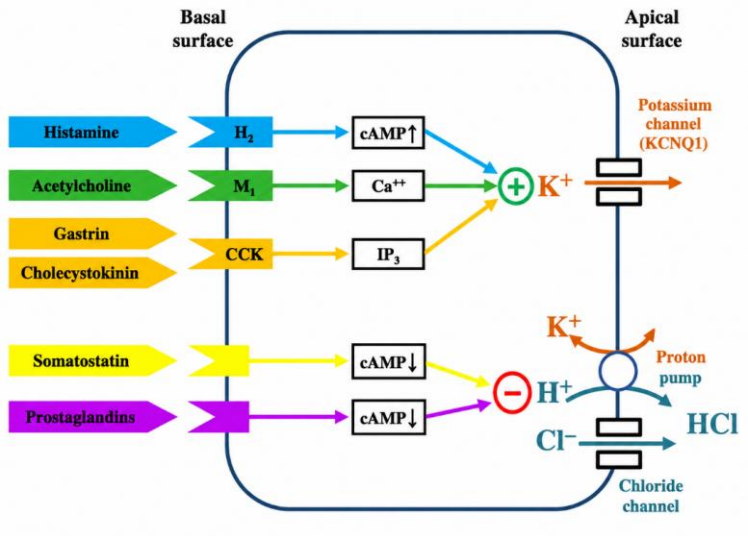
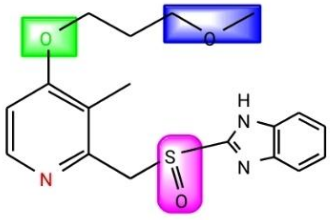


Figure 1: A simplified description of the physiology of gastric acid secretion; other compounds involved in its regulation, not shown, include ghrelin, glutamate, pituitary adenylasecyclase-activating peptide (PACAP), and serotonin (5HT).

A reduced dose of rabeprazole (10 mg od) exhibited better anti-secretory 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 first 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 [9].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 significantly 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) [7,8].

A number of researchers during recent years have investigated the occurrence of nocturnal gastric acid breakthrough (NAB), which has been defined 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 reflux symptoms and have questioned whether this phenomenon is due to a failing efficacy of PPIs over the 24 hours.

In demonstrated that rabeprazole 20 mg, administered in the morning or in the evening, significantly 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 defined 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 [10].



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

Figure 2: The IUPAC name of Rebiprazole and their side chain

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 rabeprazolevs 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 $p < 0.05$. It must be acknowledged that in Luo's study the H. pylori status was not controlled, and this factor is known to influence the duration of NAB, as for example shown by the increase of NAB following H. pylori eradication [11-12]. 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 post dose[13,14]. 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 plasma concentration are proportional to the dose ingested, time to reach Cmax and half-life are dose independent. This behavior confirms that rabeprazole does not have a saturable first-pass metabolism and it can be absorbed in high doses[15]. Neither antacids nor food influence 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 emptyin

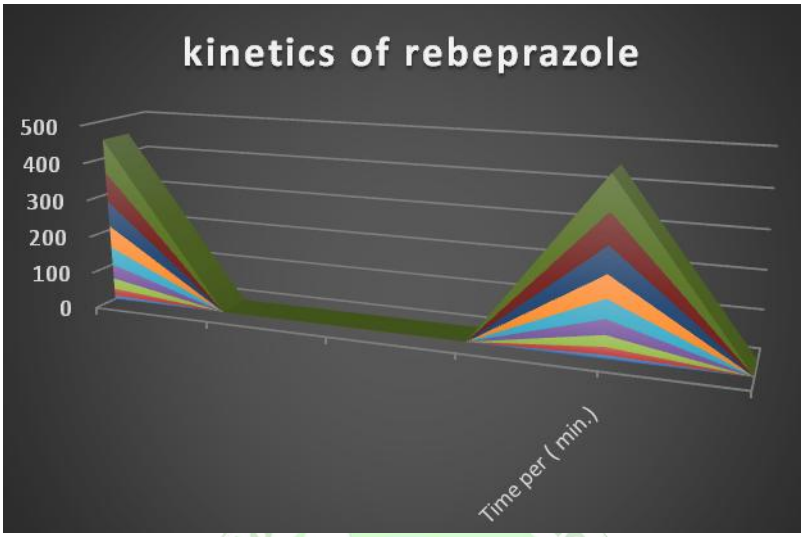


Figure: 3 releasing dose in percentage in per (min.) time.

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 [16]. This productivity 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, auto-inhibit 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 [17,18].

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 iso-enzymes 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 [19,20].

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 reflux of gastric content in the esophagus should be interpreted as a disease continuum or as different and non-communicating sub-groups 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 reflux 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 [21].

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 efficacy endpoint in studies was the continued absence of esophageal erosions or ulcerations at follow-up endoscopic examinations. An early study compared rabeprazole with placebo [22], 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, and time lost from usual activities of daily living, or antacid use. These studies reported also Kaplan-Meier probabilities for remaining free of severe daytime and night-time heartburn [23].

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 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 [24].

CONCLUSION:

Rabeprazole provides faster and more consistent acid suppression than omeprazole due to a metabolism less dependent on genetic variations. Treatment duration varies by condition, ranging from two to eight weeks for acute healing to continuous long-term management for specialized disorders. You can explore further information regarding its clinical applications and usage guidelines. Rabeprazole is a well-tolerated proton pump inhibitor. It has proven efficacy in healing, symptom relief and prevention of relapse of peptic ulcers and GORD and can form part of effective H. pylori eradication regimens. It is an important alternative to H(2) antagonists and an additional treatment option to other proton pump inhibitors in the management of acid-related disorders.

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