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Review article: the pharmacodynamics and pharmacokinetics of proton pump inhibitors – overview and clinical implications

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SUMMARY

During the past two decades, enormous changes occurred in the management of gastric acid-related diseases. First, the histamine$_2$-receptor antagonists were introduced, offering patients the first single-agent therapy that effectively reduced gastric acid secretion. Proton pump inhibitors became widely available in the early 1990s, and they generally appeared to be superior to the histamine$_2$-receptor antagonists in acid-suppressing activity, symptom control and healing. Most physicians now use proton pump inhibitors as first-line treatment for many patients with acid-peptic disorders, including erosive gastro-oesophageal reflux disease (GERD), nonerosive reflux disease (NERD) and duodenal and gastric ulcers. Although proton pump inhibitors are often thought to be interchangeable, some differences have emerged in their pharmacological properties, which may be reflected in some aspects of clinical efficacy. Such differences include potency, speed of onset and duration of pH 'holding times'. *Helicobacter pylori* has now been recognized as an important factor in the pathogenesis of acid-peptic disorders. It is clear that *H. pylori* eradication can dramatically reduce the chronicity of gastric and duodenal ulcers, and accepted therapeutic regimens for *H. pylori* eradication now include proton pump inhibitors and two or more antibiotics. Although all accepted proton pump inhibitor-based 'triple therapies' are roughly equivalent in efficacy, there is now a shortened regimen available that will potentially enhance compliance and decrease cost. This review examines the relative advantages of proton pump inhibitors vs. histamine$_2$-receptor antagonists in the context of acid suppression and in various gastric acid-related diseases. A brief overview presents the pharmacodynamics and pharmacokinetics of the proton pump inhibitors with particular attention paid to rabeprazole, one of the newer drugs in its class.

INTRODUCTION

Compared with earlier antacid therapy and anticholinergic agents, histamine$_2$-receptor antagonists represented a dramatic improvement in control of gastric acid and, consequently, in the management of acid-mediated disorders. Not only were these drugs effective, they proved to be exceptionally safe and well-tolerated. Ultimately, these features led to the conversion of prescription histamine$_2$-receptor antagonists to over-the-counter formulations, giving patients the option of self-medication. Despite the success of the histamine$_2$-receptor antagonists, there were patients whose acid-related disorders failed to respond to or required very high doses of these drugs. Furthermore, the phenomenon of histamine$_2$-receptor antagonist tolerance was recognized with implications for possible failures of chronic/maintenance histamine$_2$-receptor antagonist therapy. Proton pump inhibitors were subsequently developed, and, in most respects, have been found to be superior to histamine$_2$-receptor antagonists in their acid-suppressing ability.[1, 2] They also relieve oesophagitis symptoms and heal erosions more effectively than histamine$_2$-receptor antagonists.[3] Proton pump inhibitor

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acceptance has been broad, and proton pump inhibitor use continues almost logarithmic growth.

As a result of these changes in physician prescribing habits, particularly because they have frequently occurred in the context of a managed care environment, clinicians and healthcare administrators face a new set of issues in the selection of treatment for gastric acid-related disease. Costs of proton pump inhibitors are high, and there has continued to be some pressure to restrict proton pump inhibitor availability by making histamine$_2$-receptor antagonists 'preferred treatments' in many settings. Moreover, there is great pressure on physicians to avoid long-term proton pump inhibitor administration. Without demonstration of some 'accepted indication' for chronic proton pump inhibitor use (e.g. erosive oesophagitis), a particular number of weeks is sometimes specified for their use. There are often formulary constraints that determine availability of specific proton pump inhibitors. Even when no such mandatory restrictions are enforced, there are incentives to minimize proton pump inhibitor dosage, frequency and duration of treatment. Proton pump inhibitors do differ in several ways, and knowledge of disease pathophysiology plus proton pump inhibitor pharmacology may be quite helpful in tailoring proton pump inhibitor therapy to specific clinical settings. In general, optimal drug selection can reduce the overall cost of care while enhancing the short- and long-term outcomes of therapy.[4, 5]

There is a growing body of evidence defining the pharmacodynamic differences among proton pump inhibitors that could translate into clinical differences, which subsequently may provide some agents with unique advantages in specific clinical settings. Degree and speed of intragastric acid suppression and duration of acid suppression can and should affect the efficacy with which a drug controls symptoms and heals disease. For patients with gastric and duodenal ulcers, and in certain other limited settings, the role played by *Helicobacter pylori* in gastric acid-related diseases has changed the treatment of appropriately selected infected patients, making *H. pylori* eradication, using antibiotics in conjunction with proton pump inhibitors, an important treatment for patients with these disorders. The time to onset of antisecretory activity and extent of acid suppression can influence the efficacy of acid-labile antibiotics for *H. pylori* eradication.[2]

This article initially addresses some aspects of relative pharmacology and clinical efficacy of histamine$_2$-receptor antagonists vs. proton pump inhibitors. A brief overview presents some aspects of the pharmacodynamics and pharmacokinetics of the proton pump inhibitors and the role these features play in the clinical activity of the drugs. Particular attention will be directed to rabeprazole, one of the newer proton pump inhibitors, noted for its rapid onset of action and other potentially favourable pharmacodynamic and pharmacokinetic qualities that could optimize rapidity of acid suppression, potency and predictability of antisecretory effects in broad patient populations.[6–8]

PROTON PUMP INHIBITORS VS. HISTAMINE$_2$-RECEPTOR ANTAGONISTS

Acid suppression

Gastric acid secretion is a complex process regulated by at least three types of receptors (histamine, gastrin and acetylcholine) on the parietal cell.[9] Activation of these receptors ultimately leads to activation of the gastric acid (proton) pump, H^+K^+-adenosine triphosphatase (ATPase), which regulates acid transport and is the final common pathway to acid secretion by the cell that has been triggered by the stimulation of one or more receptors (Figure 1).[10, 11] In contrast to histamine$_2$-receptor antagonists or anticholinergic agents, which only partially inhibit histamine-, gastrin- or acetylcholine-stimulated acid secretion, proton pump inhibitors inhibit acid secretion in response to all stimulatory agents.[12] Consequently, proton pump inhibitors are exceptionally effective for the control of daytime (including meal-stimulated) acid production. Proton pump inhibitors also inhibit nocturnal acid secretion, although a variable amount of nocturnal acid breakthrough secretion occurs at night with all proton pump inhibitors. Suppression of nocturnal acidity is thought to be pivotal to duodenal ulcer healing, and severe gastro-oesophageal reflux disease (GERD) and atypical GERD can involve injury provoked by night-time gastric acid production and gastro-oesophageal reflux. Proton pump inhibitors elevate pH > 3 or > 4 (and other even more quantitative measures of acidity such as integrated gastric and oesophageal acidity) for longer time periods than do histamine$_2$-receptor antagonists. This can be crucial for the management of erosive reflux oesophagitis, as acid suppression during most of each 24-h period is important for the healing process. It has been shown that maintaining an elevated pH/decreased

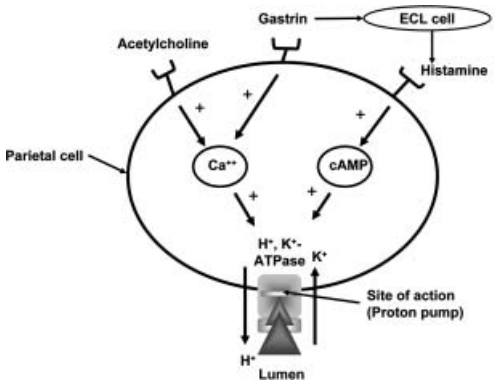

Figure 1. Gastric acid secretion is a complex process regulated by three types of receptors on the parietal cell (histamine, gastrin and acetylcholine). Activation of these receptors leads to activation of the gastric acid (proton) pump, H^+K^+-adenosine triphosphatase (ATPase), which regulates acid transport and is the final common pathway to acid secretion for these three receptors. In contrast to histamine$_2$-receptor antagonists that only partially block these receptors, proton pump inhibitors directly block the action of H^+K^+-ATPase, thereby suppressing gastric acid secretion, both basal and stimulated, regardless of the stimulus. cAMP, cyclic adenosine monophosphate; ECL, enterochromaffin-like cell. Adapted from Sachs G *et al.*[11]

acidity for longer periods is associated with higher healing rates for both peptic ulcer and reflux oesophagitis.[12] In fact, proton pump inhibitors have consistently shown greater acid suppression, higher healing rates and more improved symptom control for both GERD and peptic ulcer disease than histamine$_2$-receptor antagonists.

GERD

In the past at least, maintaining pH > 4 has been widely accepted as the benchmark for measuring the efficacy of antisecretory agents used in the treatment of pathological reflux.[13] Similarly, the healing of visibly injured mucosa correlates directly with the number of hours in a 24-h period during which intragastric pH is raised to > 4.[14] Proton pump inhibitors maintain intragastric pH > 4 between 15 and 21 h daily, whereas histamine$_2$-receptor antagonists do so for approximately 8 h daily.[14] It is thought that the superior pharmacodynamic profile of proton pump inhibitors concerning their ability to suppress basal and postprandial acid provides therapeutic benefits in both mild and severe forms of oesophagitis. Clinical trials have consistently demonstrated that proton pump inhibitors are superior to standard doses of histamine$_2$-receptor antagonists for GERD management.[13] The histamine$_2$-receptor antagonists offer a therapeutic gain of only 10–24% relative to placebo in healing oesophagitis; in contrast, proton pump inhibitors offer a therapeutic gain of 57–74% relative to placebo.[16] In addition, proton pump inhibitors have another advantage over histamine$_2$-receptor antagonists in that pharmacological tolerance has not been associated with the use of proton pump inhibitors,[17] whereas high-dose histamine$_2$-receptor antagonists do lead to relatively rapid development of tolerance.[18–21]

Results from 33 randomized clinical trials including more than 3000 patients have demonstrated healing of oesophagitis in 78% of proton pump inhibitor-treated patients and 50% of histamine$_2$-receptor antagonist-treated patients.[22] In a meta-analysis including 7635 patients with endoscopically proven oesophagitis of varying severity (grade 2 in 61.8%, grade 3 in 31.7% and grade 4 in 6.5% of patients), proton pump inhibitors provided better symptom relief and healing than histamine$_2$-receptor antagonists (Figure 2).[3] The healing speed with proton pump inhibitors was twice as fast as with histamine$_2$-receptor antagonists, with the largest gain seen early in treatment.[3] Another meta-analysis showed similar findings, with significantly higher rates of healing with proton pump inhibitors than with histamine$_2$-receptor antagonists (95% vs. 62% at week 12); this was irrespective of the grade of oesophagitis (Figure 3).[23] Although healing rates for proton pump inhibitors are superior to those of histamine$_2$-receptor antagonists, the most recent of the latter still result in more than 50% healing of erosive oesophagitis; in 242 patients with GERD, patients receiving ranitidine 150 mg twice daily had a 70% healing rate.[24]

A significant complication of GERD is Barrett's oesophagus, which is characterized by the replacement of damaged squamous epithelial mucosa with metaplastic columnar epithelium.[13, 25] Barrett's oesophagus is the single most important risk factor for oesophageal adenocarcinoma, and it has been suggested that oesophageal acid exposure plays an important role in its pathogenesis. Although the benefits of proton pump inhibitors in reducing abnormal cell proliferation and promoting healthy cell differentiation are suspected but unproved, profound acid suppression with these agents certainly produces symptomatic relief and may induce

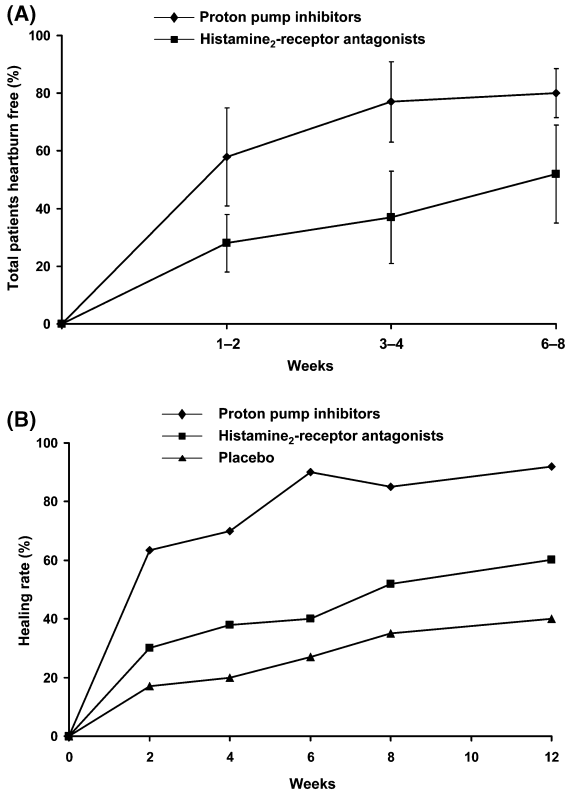

Figure 2. Heartburn relief times and healing time: meta-analysis of clinical trials of proton pump inhibitors and histamine$_2$-receptor antagonists. (A) Mean total heartburn relief corrected for patients free of heartburn at baseline (time in weeks); (B) mean total healing per evaluation (time in weeks). Adapted from Chiba *et al.*[3]

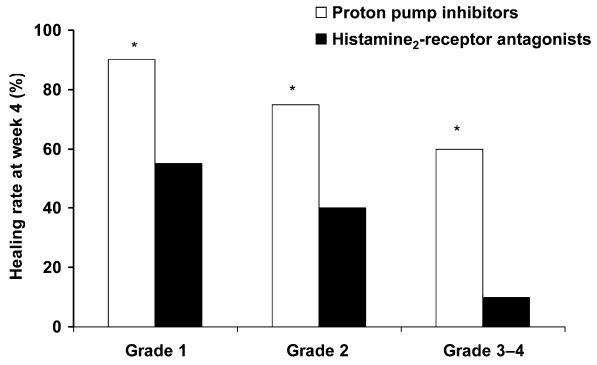

Figure 3. Meta-analysis of efficacy of proton pump inhibitors compared with histamine$_2$-receptor antagonists in the treatment of erosive oesophagitis. The proton pump inhibitors had superior healing power compared with histamine$_2$-receptor antagonists, regardless of the severity of oesophagitis (1 = less severe; 4 = most severe). *$P < 0.05$ compared with histamine$_2$-receptor antagonists. Reproduced from Jones *et al.* with permission.[23]

partial regression of metaplastic epithelium to squamous epithelium.[25]

Duodenal ulcer

Although the development and chronicity of classic duodenal ulcer has been largely attributed to *H. pylori* infection, patients with duodenal ulcer secrete more acid than healthy subjects because of increased parietal cell mass, caused at least in part by infection-induced hypergastrinaemia.[26] Nocturnal acidity appears to be an important factor in the development of duodenal ulcer; however, 24-h inhibition of acidity is a more important determinant for healing.[2] It has been demonstrated that maintaining an intragastric pH > 3 for 18–20 h each day is necessary in order to achieve healing at 4 weeks.[27]

Clinical trials have consistently demonstrated the superiority of proton pump inhibitors over histamine$_2$-receptor antagonists in producing faster healing and higher healing rates in the treatment of duodenal ulcer. Healing is achieved after 2–4 weeks with once-daily proton pump inhibitor therapy compared with 4–8 weeks using histamine$_2$-receptor antagonists.[28] A meta-analysis including 3504 patients with duodenal ulcer showed that at 2 weeks the healing rate was 61.7% with omeprazole (20 mg daily) and 46.5% with ranitidine (300 mg daily); at 4 weeks the healing rates were 87.4% and 76.5% for omeprazole and ranitidine, respectively ($P < 0.001$ at both 2 and 4 weeks).[29] Comprehensive pooled data from 384 randomized controlled clinical trials of 44 870 patients showed that a proton pump inhibitor (omeprazole) was significantly more effective ($P < 0.001$) than other classes of drugs, including histamine$_2$-receptor antagonists, in achieving duodenal ulcer healing.[30] Overall healing rates were 80.8% for omeprazole compared with 74.7% for histamine$_2$-receptor antagonists. In addition, the percentage of patients healed per week was approximately four times greater with omeprazole than with histamine$_2$-receptor antagonists (84% vs. 20%).[30] At week 4, the healing rates were significantly greater in the rabeprazole-treated patients (83% vs. 73%, $P = 0.017$), and the overall well-being with normalization was significantly higher in the rabeprazole group than in the ranitidine group (45% vs. 29%, $P = 0.003$).[31] Similar healing differences were also reported between other proton pump inhibitors (lansoprazole[32] and

pantoprazole[33]) and histamine$_2$-receptor antagonists. No studies comparing esomeprazole with histamine$_2$-receptor antagonists have been reported; however, as esomeprazole is an isomer of omeprazole, its relative efficacy in duodenal ulcer can readily be estimated.

Gastric ulcer

Most patients with gastric ulcer have normal or reduced levels of gastric acid secretion.[34] Nonetheless, suppression of gastric acid remains the mainstay of therapy for this disease.[2] As with duodenal ulcer, healing is closely related to the suppression of 24-h acidity, and maintaining gastric pH > 3 for 18–20 h a day ensures healing in 100% of patients with gastric ulcer at 8 weeks.[2, 34] Gastric ulcer takes longer to heal than duodenal ulcer; therefore, overall duration of effective treatment is an important factor in determining complete healing.[2] Therapeutic outcome in gastric ulcer is influenced by the ease of dosing and compliance with the antisecretory therapy during the entire length of treatment.

Clinical trials have consistently demonstrated higher healing rates of gastric ulcer with proton pump inhibitors than with histamine$_2$-receptor antagonists.[2] A therapeutic gain of 9.9% on the healing rates of gastric ulcer at 4 weeks and 6.7% at 8 weeks was reported with omeprazole (20 mg daily) compared with ranitidine (300 mg daily).[29] Similar superior healing results were also reported for pantoprazole vs. ranitidine,[33] rabeprazole vs. famotidine[35] and lansoprazole vs. various histamine$_2$-receptor antagonists.[36] As gastric ulcers may be more mucosal defence–related than duodenal ulcers, the relative increase in efficacy achieved by proton pump inhibitors vs. histamine$_2$-receptor antagonists is not quite as dramatic in gastric ulcers as has been repeatedly demonstrated in duodenal ulcer disease.

H. pylori *infection*

Currently, it is well accepted that *H. pylori* infection is an important factor in the development of peptic ulcer disease.[37] It is strongly recommended that all patients with gastric ulcer or duodenal ulcer who are demonstrably infected with *H. pylori* be treated with a proton pump inhibitor along with antibiotics, regardless of whether they are experiencing the initial manifestations of the disease or a recurrence.[38] Several studies have demonstrated that proton pump inhibitors in combination with antibiotics (dual [one antibiotic] or triple [two antibiotics] therapy) produce a synergistic effect in the eradication of *H. pylori* and are more effective than histamine$_2$-receptor antagonists.[26, 28] By increasing the intragastric pH, proton pump inhibitors may reduce the degradation of acid-labile antibiotics or possibly enhance antibiotic absorption, secretion or tissue penetration/distribution.[39] *In vitro* studies have also demonstrated the inhibitory effect of proton pump inhibitors on the growth of *H. pylori*, with minimum inhibitory concentrations ranging from 6.25–12.5 mg/L for omeprazole, to 3.1–6.25 mg/L for lansoprazole and 1.6–3.1 mg/L for rabeprazole.[40] However, it is not known whether this inhibitory potential contributes to the synergistic effect. Proton pump inhibitor–based triple therapies are generally considered the best available treatment in the eradication of *H. pylori*.[39]

CHARACTERISTICS THAT CAN AFFECT THE CLINICAL ACTIVITY OF A PROTON PUMP INHIBITOR

Because the severity of GERD symptoms is closely correlated with exposure to gastric acid (Table 1),[2, 41] the superior efficacy of proton pump inhibitors in controlling heartburn and other reflux symptoms could be explained by the greater degree and duration

Table 1. Severity of gastro-oesophageal reflux symptoms correlated with acid reflux exposure time. Adapted from Huang and Hunt[2] with permission; data from Joelsson and Johnsson[41]

Group	Acid exposure time (% of 24-h period)	Reflux symptoms (≥ grade 2)
Healthy controls ($n = 50$)	1.1	0
Patients with no oesophagitis ($n = 127$)	3.4*	63/127 (50%)
Patients with oesophagitis ($n = 63$)	10.6*	42/63 (67%)

*Significant difference vs. healthy controls.

of gastric acid suppression provided by proton pump inhibitors compared with histamine$_2$-receptor antagonists.[2, 3, 12, 34, 42, 43] Therefore, any pharmacodynamic differences observed among proton pump inhibitors, including extent, speed and duration of intragastric acid suppression, might well create differing clinical profiles and impact selection of one vs. another proton pump inhibitor depending on the therapeutic requirements of individual patients. Furthermore, suppression of intragastric acidity consistently predicts healing across the spectrum of gastric acid-related diseases.[44] Thus, if a proton pump inhibitor provides a greater degree or a longer duration of acid suppression (pH holding time) in a specific setting compared with alternative proton pump inhibitors, that proton pump inhibitor should have the potential for more reliable symptom control and healing.

Other pharmacological properties that can help in proton pump inhibitor selection are the metabolic pathways, which can be affected by food intake (food/drug interactions) or other drug treatment (drug–drug interactions). Bioavailability and elimination are also important as they can dictate dosing in specific populations such as the elderly.[45, 46] These features can contribute to a drug's overall pharmacological specificity and clinical reliability in treating gastric acid-related disorders.

Pharmacodynamic influences

The agents in the proton pump inhibitor class are all very effective. Reviews of studies involving the five established proton pump inhibitors, omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole, point largely to clinical equivalence over the full course of therapy for gastric acid-related diseases.[47–49] However, some differences have been observed that may translate into treatment advantages or benefit for individual proton pump inhibitors in specific clinical situations.

Onset of action Proton pump inhibitors exert their acid-suppressive effect by blocking the H^+K^+-ATPase enzyme, which is responsible for inducing acid secretion in the stomach. An *in vitro* study examined the relative ability of four proton pump inhibitors, omeprazole, lansoprazole, pantoprazole and rabeprazole, in inhibiting the activity of this enzyme.[50] Results showed that in prepared hog gastric vesicles, rabeprazole inhibited the gastric H^+K^+-ATPase faster than the three other proton pump inhibitors (Figure 4). Enzyme inhibition was almost complete within 5 min of rabeprazole exposure compared with 30 min for omeprazole and lansoprazole; pantoprazole had achieved only 50% inhibition by the end of the 50-minute test.

In a recent *in vivo* study, subjects received single daily doses of rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, omeprazole 20 mg capsule, omeprazole 20 mg multiple unit pellet system (MUPS) tablet or placebo. Results revealed that for the majority of subjects, the onset of action of all the tested drugs was within 2 h (lansoprazole 1.0 h; omeprazole MUPS: 1.25 hours; omeprazole capsule: 1.5 h; and rabeprazole and pantoprazole: 1.75 hours; $P = 0.6$).[51] However, rabeprazole achieved the highest 24-h median pH (3.4) within the first day. This pH elevation was significantly higher compared with the other proton pump inhibitors and placebo ($P \leq 0.04$), which indicated a faster onset toward maximum effect with rabeprazole compared with the other proton pump inhibitors.

This pronounced first-day effect seen with rabeprazole has been previously observed.[52] Although the time of onset and duration of antisecretory activity were similar for omeprazole 20 mg and rabeprazole 20 mg, the median extent of inhibition of intragastric acidity produced by the first dose of rabeprazole was almost twice that produced by the first dose of omeprazole (24-h integrated acidity with rabeprazole was 61 ± 5% vs. 31 ± 7% with omeprazole; $P < 0.0001$). This superior inhibition with rabeprazole compared with omeprazole remained significant ($P < 0.05$) 8 h after the first dose.[52]

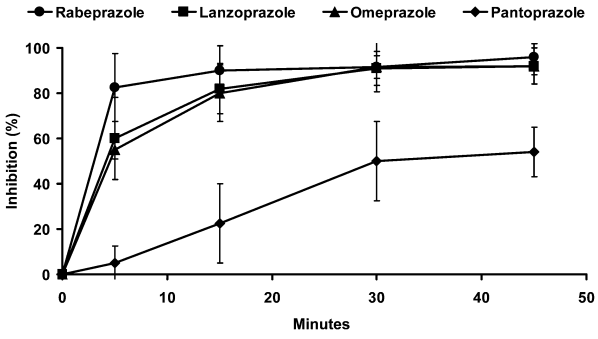

Figure 4. *In vitro* inhibition over time of the H^+K^+-adenosine triphosphatase enzyme in hog gastric vesicles achieved during exposure to omeprazole, lansoprazole, pantoprazole and rabeprazole. Adapted from Besancon *et al.*[50]

pH holding time As mentioned earlier, there is a correlation between the exposure time to gastric acid and the symptoms of acid-related disorders. Therefore, the longer any antisecretory drug maintains a high pH (> 3 or, better, > 4) after dosing, the better the symptom relief and the faster the healing. The duration of this pH increase over a 24-h period is known as the pH holding time. Most of the acid-proton pump inhibitor effects result in an increase of pH ≥ 3. For example, in a review comparing proton pump inhibitor trials, rabeprazole 20 mg therapy was associated with superior pH holding time compared with omeprazole 20 mg ($P < 0.001$).[53] The response to lansoprazole was also greater than that with omeprazole, but this agent was often administered at higher doses (lansoprazole 30–60 mg compared than that with omeprazole 20 mg). Pantoprazole appeared to be approximately equal in potency to omeprazole.[53] In some studies, esomeprazole has shown superior pH holding times compared with other proton pump inhibitors. However, esomeprazole was used at a 40-mg dose, whereas the others were used at lower doses (omeprazole and rabeprazole 20 mg; lansoprazole 30 mg). Only pantoprazole was compared on a mg/mg basis.[54]

In the study comparing rabeprazole with four other proton pump inhibitors mentioned previously, a significantly greater pH holding time was shown with rabeprazole on the first day of dosing.[51] Figure 5 illustrates the percentage of time with pH > 4 using rabeprazole, lansoprazole, pantoprazole, omeprazole, omeprazole MUPS and placebo. The percentage of time with pH > 4 was significantly greater with rabeprazole than with all other proton pump inhibitors or placebo ($P \leq 0.04$), and significantly greater with lansoprazole than with pantoprazole 40 mg, omeprazole 20 mg capsule and placebo ($P \leq 0.03$). In addition, percentage of time with pH > 3 was significantly longer with rabeprazole than with placebo and all proton pump inhibitors except lansoprazole ($P \leq 0.04$). Rankings for holding time were consistent during both daytime and night-time hours.[51]

In a recent five-way crossover trial investigating pH holding times for five proton pump inhibitors,[55] patients received each proton pump inhibitor for 5 consecutive days with a 10–24-day washout between each treatment. The percentage of time pH > 4 over 24 h was measured for day 5, resulting in the greatest holding time for esomeprazole, followed by rabeprazole, omeprazole, lansoprazole and pantoprazole. It should be noted that these results are for day 5, not day 1, and therefore cannot be directly compared with results from the study mentioned by Pantoflickova *et al.* in the previous paragraph[51] to determine how esomeprazole compares with the other proton pump inhibitors for onset of activity. The multiple crossover trial by Miner *et al.* specifically excluded measurement of oesophageal acidity or any assessments of any acid status during the first 4 days of proton pump inhibitor administration.

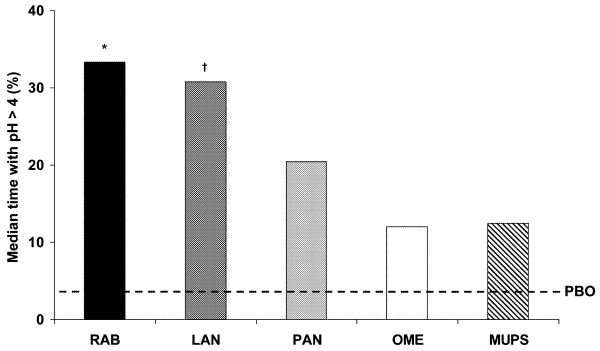

Figure 5. Comparison of four proton pump inhibitors in percentage of time with pH > 4 after a single daily dose. LAN, lansoprazole 30 mg; MUPS, omeprazole 20 mg multiple unit pellet system (MUPS); OME, omeprazole 20 mg; PAN, pantoprazole 40 mg; PBO, placebo; RAB, rabeprazole 20 mg. *$P \leq 0.004$ vs. all other proton pump inhibitors; †$P \leq 0.03$ vs. pantoprazole and omeprazole. Adapted from Pantoflickova *et al.*[51]

Pharmacokinetic influences

Metabolism For the proton pump inhibitors omeprazole, lansoprazole, pantoprazole and esomeprazole, certain hepatic isoenzyme pathways, notably cytochrome P450 (CYP)2C19, make a more significant contribution to drug metabolism (however, this is not the case with rabeprazole). In particular, among patients who are genotypically rapid, or 'extensive', metabolizers, proton pump inhibitors with significant CYP2C19 metabolism tend to yield lower plasma levels and, thus, have lower efficacy.[56, 57]

The contribution of the CYP2C19 pathway varies in the metabolism of different proton pump inhibitors.[58–60] Rabeprazole is unique among proton pump inhibitors: unlike the metabolism of omeprazole, esomeprazole, lansoprazole and pantoprazole, isoenzymatic CYP2C19 and CYP3A4 pathways are secondary for rabeprazole metabolism.[60, 61] Instead, a nonenzymatic pathway, formation of a thioether compound by sulphoxide

reduction, plays a predominant role in rabeprazole metabolism.[60] The relative impact of the CYP2C19 pathway on metabolism of the proton pump inhibitors has been reported to be omeprazole = esomeprazole > pantoprazole > lansoprazole > rabeprazole.[60, 61] Esomeprazole (*S*-isomer) is metabolized more slowly and reproducibly than the *R*-isomer and omeprazole (mix of both *S*- and *R*-isomers). Hence, esomeprazole may produce higher plasma concentrations for longer periods and inhibit gastric acid production more effectively and for a longer period of time. However, esomeprazole has a metabolic pathway similar to that of omeprazole.[62, 63]

Drug interactions Oxidative hepatic metabolism via the CYP450 system is an important determinant of drug–drug interactions; therefore, certain proton pump inhibitors have the potential for interactions. In practice, however, proton pump inhibitors differ in the number of interactions they exhibit.

Three factors help to predict drug–drug interactions via CYP metabolism: degree of contribution of a particular CYP isoenzyme to metabolism of both drugs, degree of affinity of the drugs for the particular isoenzyme and concentrations of the drugs in hepatic cells after dosing. For example, if two drugs are metabolized extensively by CYP2C19 (e.g. omeprazole and diazepam), competitive inhibition would be expected. The drug with less affinity to CYP2C19 would be the one with a significantly inhibited metabolism.

It has been postulated that among proton pump inhibitors, omeprazole has the most marked competitive inhibitory potential at CYP2C19; the inhibitory effect of omeprazole at CYP2C19 is also increased in patients who are extensive metabolizers by this pathway.[64, 65] It has been shown that diazepam clearance decreases 26% during treatment with omeprazole in extensive metabolizers and not at all in poor metabolizers;[64] thus, clinical observation of a diazepam interaction stems from those in the patient population who are extensive metabolizers.[61, 65, 66]

In contrast, rabeprazole has a low potential for CYP450-mediated drug–drug interactions[61, 67] because the CYP450 pathway is secondary in the metabolism of rabeprazole,[60, 61] which is instead metabolized through a nonenzymatic pathway.[60] Furthermore, a study has demonstrated that rabeprazole does not alter the pharmacokinetics of diazepam in either extensive or poor metabolizers, whereas omeprazole significantly decreases the mean clearance of diazepam in extensive metabolizers.[68] This further shows that rabeprazole has a lower potential for CYP450-mediated drug–drug interactions than omeprazole.

CONCLUSION

The pharmacodynamic and pharmacokinetic features of proton pump inhibitors offer clinicians two more areas for drug comparison. Comparative data on the degree of acid suppression and drug metabolism can be useful in making choices among proton pump inhibitors for the individual patient. Of particular interest are the differences in median pH and pH holding time that individual proton pump inhibitors exhibit. Such pharmacodynamic differences allow the clinician to select drugs that suppress acid most powerfully and most quickly, an important consideration because healing and symptom control in gastric acid-related diseases correlate well with acid suppression. In addition, metabolic features of proton pump inhibitors help predict which agents are likely to be less effective when administered to genotypically extensive metabolizers. Metabolism also influences drug–drug interactions, which vary among proton pump inhibitors. Rabeprazole compares favourably with other proton pump inhibitors in terms of these parameters. It provides acid suppression that appears to be more potent after only 1 day of treatment than other proton pump inhibitors, and it also presents less risk of reduced antisecretory efficacy in patients who are extensive metabolizers. The impact of this property is a high degree of predictability of efficacy, a degree that may be different from the earlier proton pump inhibitors.

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