Proton Pump Inhibitory Therapy: Then and Now

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Proton pump inhibitors (PPIs) have been established as the new “gold standard” for traditional acid-inhibitory treatment of the so-called “peptic” diseases. Due to the high antisecretory and ulcer-healing potency of omeprazole, no major improvements of the efficacy in ulcer healing and pain relief can be expected. Pantoprazole, as a further development in PPIs, is characterized by improved pharmacokinetic behavior as well as by higher tissue selectivity and binding specificity and by a very low potential to interact with the cytochrome P450 enzyme system. These characteristics may provide the basis for a low potential for side effects and for a more favorable interaction profile, although the clinical relevance of these potential advantages remains to be proven. Reflux esophagitis will also remain a domain for the traditional use of PPIs in the future. However, in the treatment of gastroduodenal ulcers, the acid inhibitory potential of PPIs will be used mainly to facilitate the eradication of H. pylori.

INTRODUCTION

Since Schwarz’s dictum “no acid — no ulcer” was coined in 1910 [1], treatment of reflux esophagitis and gastro-duodenal ulcers has been awaiting modalities providing effective control of gastric acid secretion. It was not until the late 1960s that antacids became available. These, however, just partially neutralized gastric acid that already had been secreted. Thus, symptom control and healing rates were unsatisfactory. These disappointing results, together with the inconvenience of frequent drug intake, resulted in poor patient compliance.

It was only logical that antacids were rapidly replaced by antagonists acting at the parietal cell histamine H2 receptors. For the first time these drugs provided effective inhibition of production and release of gastric acid via a pharmacologically well-defined mechanism and became the gold standard of acid inhibitory therapy in the late 1970s. However, H2 receptor antagonists (H2RAs)b do not block parietal cell stimulation by agonists other than histamine, e.g., vagal acetylcholine interacting with parietal cell M3 receptors. Moreover, H2RAs are far more effective in inhibiting nocturnal than day-time acid secretion. Furthermore, the efficacy of these drugs declines after several days of treatment.

These shortcomings were overcome when proton pump inhibitors (PPIs) became available for clinical use in the late 1980’s. Their superior antisecretory potency provided an excellent basis to replace H2RAs as the gold standard in the therapy of acid-related diseases. In the following, clinical results of treatment with PPIs, which have established these compounds as the drugs of choice, will be reviewed. Thereafter, potential advantages of further developments in PPIs will be evaluated. Finally, rationales will be discussed for the use of PPIs in a new indication, eradication of the bacterium Helicobacter pylori from the gastric mucosa.

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bAbbreviations: H2RA, H2 receptor antagonists; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug.
THEN: CLINICAL RESULTS

Reflux esophagitis

PPIs are superior to H2 RAs in healing acute erosive reflux esophagitis (Savary and Miller grades II-IV). In numerous studies the healing rates after four, eight and 12 weeks of daily treatment with PPIs were 60, 85 and 95 percent; the corresponding healing rates with standard doses of H2 RAs were 35, 50, and 65 percent [2-6], the majority of patients being classified as grades II (II-III) according to Savary and Miller. PPIs have proven to be especially valuable in the treatment of reflux esophagitis refractory to treatment with H2 RAs, since within 8 to 12 weeks of daily treatment with 40 mg omeprazole healing was achieved in almost all patients [7]. Even more important to the patient, pain relief occurs faster upon treatment with PPIs than with H2 RAs. Complete freedom from pain was reported by 65 percent, 85 percent, and 95 percent of patients treated with omeprazole for four, eight and 12 weeks, while the corresponding data of patients on H2 RAs were 30, 50 and 60 percent [2-6]. With the PPIs that were developed later, lansoprazole and pantoprazole, similar results have been obtained as with omeprazole with respect to healing and symptom relief in the acute treatment of reflux esophagitis [8-10]. However, it must be kept in mind that with the later developed drugs the number of patients studied is considerably lower than with omeprazole, especially when the focus is on severe esophagitis.

Placebo-controlled studies have shown that, when treatment is stopped after healing of acute reflux esophagitis, the relapse rate is about 65 percent per year in unselected, primary-care populations [11-13] and 82 percent per six months in selected, i.e., H2 RA-refractory, patients [14]. Maintenance therapy with H2 RAs is not superior to placebo [11, 12, 15] and significantly less effective than prophylaxis with PPIs [11, 16-19]. In a primary care population, symptomatic remission was maintained over 12 months in 72 percent, 62 percent and 45 percent of patients on 20 mg omeprazole daily, 10 mg omeprazole daily and 150 mg ranitidine twice daily, respectively [20]. The difference between the 10 and 20 mg omeprazole dose narrowly missed statistical significance (p = .06) when symptomatic relapses were evaluated [20]; however, the higher omeprazole dose appeared to be significantly (p = .003) [20] or at least numerically [21] more effective in preventing endoscopic relapses, the remission rates after 12 months being 77 percent, 58 percent and 46 percent, respectively, for 20 mg omeprazole daily, 10 mg omeprazole daily and 150 mg ranitidine twice daily [20]. As expected, relapses are more frequent in selected, i.e., H2 RA-refractory, patients apparently requiring a more intense antisecretory treatment. In these patients endoscopic remission rates of 67 percent [22] and 10-25 percent [11, 12, 15-18] were observed after 12 months on prophylactic treatment with standard doses of omeprazole or ranitidine, respectively. Based on a long-term observation of selected patients initially refractory to healing with H2 RAs, life-table analysis revealed that after five years on continuous prophylaxis with omeprazole (20 mg o.d.) 55 percent were still in remission [23]. The prophylactic effect of PPIs is independent of the grade of reflux esophagitis prior to the initial treatment, initial healing dose of PPIs, and of smoking habits [17, 23]. Continuous maintenance treatment is superior to discontinuous approaches, e.g., weekend therapy (Friday, Saturday, Sunday) [16, 19, 24-26]. In maintaining remission, the prokinetic cisapride was more effective than ranitidine but significantly less effective than omeprazole [27]. On the other hand, the efficacy of ranitidine was improved by combination with cisapride; however, even this combination was less effective than omeprazole alone, the prophylactic effect of which was not significantly increased by cisapride [27].

Peptic strictures complicating reflux esophagitis (Savary and Miller grade IV) tend to relapse at a high frequency (about 50 percent within 12 months) [28, 29]. Following
dilatation, relapse prophylaxis with H2RAs has yielded disappointing results [30, 31]. On the other hand, omeprazole (20 mg daily) reduced the need for repeat dilatation by more than 50 percent (0.48 per year) when compared to ranitidine (150 mg twice daily) (1.08 repeat dilatations per year) [32]. Omeprazole was significantly more effective than ranitidine in relieving symptoms (freedom from dysphagia (76 vs. 64 percent); acceptance of normal diet (83 vs. 69 percent); increase in median body weight (1.9 vs. 0.4 kg) [32]. This study confirmed earlier disappointing results with H2RAs and the superiority of PPIs in preventing repeat dilatation [33].

**Gastric ulcers**

PPIs have been established as superior to H2RAs in the treatment of gastric ulcer. In three randomized double-blind studies [34, 35, 36], healing rates after four and eight weeks of treatment were 73 percent and 92 percent with omeprazole 20 mg every morning, and 62 percent and 86 percent with twice-daily ranitidine according to the per-protocol analysis. Likewise, omeprazole was superior to cimetidine [37]. Continuing intake of NSAIDs resulted in slightly lower four-week healing rates with omeprazole (61 percent) and ranitidine (53 percent) [34]. Symptom relief was significantly faster in patients on omeprazole than in those on H2RAs [34-37].

With respect to healing rates and symptom relief similar superiority, over H2RAs has been observed with pantoprazole (40 mg every morning) and lansoprazole (30 mg every morning) [38, 39] while these later developed PPIs were equally effective as omeprazole [40, 41].

**Duodenal ulcers**

The superiority of PPIs over H2RAs has also been established in the treatment of duodenal ulcer. According to per-protocol analysis of double-blind randomized trials, healing rates after two and four weeks of treatment were 64 percent and 92 percent with omeprazole 20 mg every morning. and 48 percent and 80 percent with ranitidine 150 mg twice daily [42-49] or 300 mg at night [50-57]. Likewise, omeprazole was superior to cimetidine [58-63]. In the identical studies, omeprazole proved to be significantly more effective than H2RAs in inducing overall symptom relief as well as daytime and nighttime pain relief [50-63].

A similar pattern of superiority was observed in trials comparing pantoprazole or lansoprazole with H2RAs [64,65]. On the other hand both later developed PPIs were equally effective as omeprazole [66,67].

In summary, PPIs speed up the healing process of gastric and duodenal ulcers more effectively than H2RAs. The latter class of drugs is also capable of healing almost all benign gastric ulcers, however, a significantly longer time is needed to achieve healing and symptom relief.

**Refractory peptic lesions**

Esophageal, gastric and duodenal lesions that do not heal on prolonged administration or increased doses of H2RAs are regarded refractory to treatment by H2RAs. These lesions require the higher acid inhibitory potency provided by PPI treatment. Ömeprazole [68], pantoprazole [69] and lansoprazole [70] were shown to rapidly heal all H2RA-refractory peptic lesions within 12 weeks, and most of them within four weeks. Thus, nowadays any peptic lesions should not be regarded refractory unless they do not heal upon PPI treatment. Such lesions are extremely rare and in most cases attributable to intake of salicylates, rarely to rapid PPI metabolism.
Gastrinoma (Zollinger-Ellison Syndrome)

Even more than H₂RA-refractory lesions, gastrinoma patients represent the ultimate test of the efficacy of acid-inhibitory therapy. These patients are characterized by excessive gastrin secretion from endocrine tumors maintaining a continuous maximal stimulation of acid production, which results in severe reflux esophagitis and multiple and frequently recurrent ulcers of the upper gastrointestinal tract. H₂RAs were the first drugs to effectively inhibit acid secretion in these patients. However, there are several disadvantages with H₂RA treatment of Zollinger-Ellison syndrome: The dose requirements are extremely high in some patients, several of them needing additional anticholinergics; H₂RAs need to be administered every four to six hours, and the dose needs to be increased every year in most gastrinoma patients. These disadvantages were overcome by the use of PPIs. By far, the most experience has been accumulated with omeprazole. Effective inhibition of acid secretion (i.e., reduction of basal acid output below 10 mEq/hr in the last hour before the next dose of omeprazole) is achieved within few days [71]. For each individual patient, the appropriate initial dose must be identified by upward titration and corresponds well with basal and maximal acid outputs as well as with the dose of H₂RAs required before starting omeprazole [71]. Patients are usually started on 60 mg of oral omeprazole. If after 23 hr (i.e., one hr before the next dose is to be taken) inhibition is still insufficient, the dose is increased. Doses of 120 mg omeprazole and above per day may be necessary for initial treatment. If even these doses fail to sufficiently inhibit acid secretion they should be split and administered as two portions in the morning and at night [71]. However, once control of acid output is achieved omeprazole doses should be gradually reduced to 20 mg daily or twice daily. This strategy is successful in 68 percent of all gastrinoma patients, in 75 percent of those doing well on an o.d. regimen, and in 54 percent of patients requiring twice daily dosing [72]. Effective inhibition of acid secretion in gastrinoma patients has also been reported for lansoprazole [73], while data with pantoprazole are lacking.

NOW: ADVANTAGES OF FURTHER DEVELOPMENTS IN PPIs

Since the late 1980s omeprazole, the first PPI to be clinically used, became the new gold standard for the treatment of acid-related diseases. What advantages should further developments in substituted benzimidazoles therefore have to offer? Since the efficacy of omeprazole with respect to inhibition of acid secretion and healing rates can hardly be overcome, efficacy is unlikely to be an advantage rendering new PPIs even more attractive than omeprazole. Rather, further developments in PPIs qualify by improved pharmacokinetic properties as well as by selectivity and specificity.

Pharmacokinetics

The absorption of omeprazole and lansoprazole from enteric-coated granule formulations is variable [74, 75]. Moreover, lansoprazole absorption is decreased by concomitant oral food intake [75, 76]. In contrast, pantoprazole, when directly compared with omeprazole, produced clearly smaller variations in serum concentrations after oral administration in the form of enteric-coated tablet [77, 78]. Moreover, unlike omeprazole, absorption of pantoprazole did not change after seven consecutive days of administration [77]. This holds also for the 30 and 60 mg doses, but not for the 10 and 20 mg doses of lansoprazole [79]. Thus, pantoprazole is characterized by constant pharmacokinetic parameters upon repeated once-daily dosing over one week [80]. These properties of pantoprazole and lansoprazole (at the 30 mg dose, not at other doses) are the basis for a constantly high bioavailability [80, 79] while omeprazole is characterized by a lower initial bioavailability increasing over the first week of treatment [81, 82].
Pantoprazole revealed clear-cut dose-linearity after oral, as well as intravenous, administration, as determined from serum concentrations and primary pharmacokinetic parameters (area under curve, maximal plasma concentration) [83]. On the other hand, lansoprazole and omeprazole revealed non-linear pharmacokinetics as evidenced by a more than proportional increase in the area under curve and maximal plasma concentrations upon increasing doses [79, 84-86]. The non-linear pharmacokinetics of omeprazole and lansoprazole, however, apparently does not cause any clinically relevant problems.

**Improved pH-stability**

All currently available PPIs are substituted benzimidazoles and weak bases, which, as parent compounds, freely enter and leave cells unless they are protonated in acidic cell compartments. Protonation results in trapping and concentration of the charged compound, followed by activation of the drug, which is now capable of inhibiting the acid-producing parietal cell enzyme, H⁺K⁺-ATPase. Ideally, protonation of PPIs should occur selectively at very low pH levels reached only in parietal cells, while at pH levels above 2 no protonation should occur. This would make sure that PPIs are activated only in parietal cells where they are expected to be effective, while in other tissues, activation of PPIs would be prevented.

Although to date no PPI fulfills these ideal criteria, pantoprazole is closer than other PPIs. This drug exhibits the slowest protonation, i.e., activation, at slightly acidic levels of pH above 2, especially at pH levels up to 5.0, [87], which may be reached temporarily in tissues others than parietal cells. In accordance with these data, in vitro activation of pantoprazole at pH above 3 levels off significantly faster than activation of omeprazole and lansoprazole [88]. As a consequence, at pH 5.0 activation of pantoprazole is down to about 25 percent while 55 percent of omeprazole and lansoprazole are still activated [88]. Likewise, the potency of pantoprazole to inhibit acid production in isolated gastric glands increases markedly with the internal acidification of the glands in response to increasingly effective stimuli, a pattern not observed with omeprazole and lansoprazole [89]. The higher selectivity of pantoprazole for the parietal cells may reduce the potential of undesired activation and side effects in other tissues, although until now no such side effects of omeprazole or lansoprazole have been identified unequivocally.

On the other hand, at the highly acidic pH levels reached in parietal cells, pantoprazole is activated at the same rate as are omeprazole and lansoprazole. Thus, the acid-inhibitory capacity of pantoprazole in parietal cells is not compromised by the diminished protonation at higher pH levels.

**Selective binding to the proton pump**

Binding of radioactively labeled PPIs to trypsin-generated fragments of the H⁺K⁺-ATPase identified the cysteine residues within the enzyme molecule to which the drugs bind covalently, thereby irreversibly inhibiting the enzyme's activity. While the Cys₈₁₃ residue in the membrane-spanning segment M₅/M₆ is the target of all three available PPIs, omeprazole (Cys₈₉₂ in M₇/M₈) and lansoprazole (Cys₈₉₂ in M₇/M₈ and Cys₃₂₁ in M₃/M₄) bind to additional targets [90, 91]. Thus, binding to Cys₈₁₃ in M₅/M₆ apparently is crucial for inhibiting the H⁺K⁺-ATPase.

To date, pantoprazole is the only PPI selectively binding to this cysteine residue. Additional binding of omeprazole and lansoprazole to Cys₈₉₂ and Cys₃₂₁ does not appear to be related to the specific acid-inhibitory effect of these substituted benzimidazoles. Undesired effects secondary to binding of omeprazole and lansoprazole to these additional cysteine residues have not been identified.
Interaction with the cytochrome \( P_{450} \) enzyme system

Pantoprazole has a significantly lower potential than omeprazole and lansoprazole to interact with the cytochrome \( P_{450} \) system [92]. This issue is discussed in a separate contribution to this symposium.

Advantages of further developments in PPIs: summary

Compared to omeprazole and lansoprazole, pantoprazole is characterized by improved pharmacokinetics and pH-stability, selective binding to the crucial cysteine residue within the \( \text{H}^+\text{K}^+\text{-ATPase} \) molecule, and a very low potential to interact with the cytochrome \( P_{450} \) enzyme system. Although it may be desirable to use a drug with these characteristics, it must be kept in mind that the safety standard of omeprazole and lansoprazole is also very high. No serious side effects have become apparent ever during almost one decade of clinical use of omeprazole in numerous patients.

NOW: RATIONALES FOR THE USE OF PPIS IN ERADICATION OF \textit{H. pylori}

The horizon of indications for the PPIs is extensively widening since it became clear that these drugs can be successfully used not only in the conventional acid-inhibitory treatment of reflux esophagitis and gastroduodenal ulcers, but also in the eradication of \textit{H. pylori}. The traditional concept of gastro-duodenal ulcer disease as a “peptic” disorder has been revolutionized by the recognition of \textit{H. pylori} as an essential etiological factor. The dictum “No acid — no ulcer” had to be expanded to “No acid and no \textit{H. pylori} — no ulcer.” Monotherapy with acid-inhibiting drugs heals ulcers, but fails to eradicate \textit{H. pylori}. Thus, this prerequisite for subsequent ulcer relapses persists in the gastric mucosa, unless it is eradicated by other treatments. These are neither monotherapies nor combinations of antibiotics as such regimens are successful in only a minority of patients. However, addition of acid-inhibiting drugs, especially PPIs, dramatically increases the eradication success of antibiotic regimens, especially those containing clarithromycin, amoxicillin and/or metronidazole [93, 94]. But how might PPI-treatment eliminate the conditions for colonization of the gastric mucosa by \textit{H. pylori}?

Several hypotheses have been proposed: \textit{In vitro}, all PPIs exhibit antimicrobial activity against \textit{H. pylori}. However, \textit{in vivo} PPIs fail to eradicate the bacterium; moreover, \textit{H. pylori} does not provide an acidic compartment in which PPIs could be protonated and activated. Thus, the direct antimicrobial effect of PPIs does not appear to contribute to the favorable effect of these drugs \textit{in vivo}. On the other hand, PPIs may cause a loss of the acidic microenvironment at the epithelial surface where \textit{H. pylori} is found directly under the mucus layer. Moreover, antibodies directed against \textit{H. pylori} may be protected against acid/pepsin-induced degradation when the intra-gastric pH is elevated due to PPI treatment. Finally, such treatment may provide optimal conditions for neutrophil function in the gastric mucus bicarbonate layer. None of these hypotheses have been unequivocally proven or disproven. Thus, interest is focusing on potentiating interactions between antibiotics and acid-inhibitory therapy.

Increased gastric mucosal concentration of antibiotics?

It is tempting to speculate that PPI-induced elevation of gastric pH may increase the mucosal concentration of antibiotics. However, in the mucosa of the corpus and antrum omeprazole (20 to 80 mg/day) failed to increase the concentration of amoxicillin [95, 96], an antibiotic widely used for \textit{H. pylori} eradication.
Increased bioavailability of antibiotics?

Another possibility would be that PPIs and antibiotics would mutually increase their bioavailability. Again, this hypothesis was disproven. The bioavailability of amoxicillin under placebo conditions was not increased by addition of omeprazole 20 mg nor was the bioavailability of omeprazole increased by addition of amoxicillin, clarithromycin or metronidazole [95, 96]. Likewise, increasing the omeprazole dose to 40 and 80 mg had no effect on the bioavailability of amoxicillin.

Increased gastric release of antibiotics?

To be active against *H. pylori*, antibiotics should be present at high concentrations between the gastric epithelial surface and the mucus layer. The effect of amoxicillin against *H. pylori* is considered mainly a systemic effect not locally provided by luminal-ly acting drugs. Since *H. pylori* is rarely found within the gastric epithelium but rather on the epithelial surface directly under the mucus layer, amoxicillin would reach the highest concentration at the bacteria themselves if the gastric mucosa would actively secrete the systemically circulating drug. In fact, after i.v. injection amoxicillin is secreted into the gastric juice, the secretion being threefold increased after administration of omeprazole (40 mg twice daily.) [97]. Thus, the PPI might potentiate the amoxicillin effect against *H. pylori* by increasing gastric mucosal release of the antibiotic.

Adjustment of gastric pH to levels appropriate for optimal activity of antibiotics?

In vitro, the activity of several antibiotics against *H. pylori* is increased when the pH is elevated from 5.5 to 7.5 [98, 99]. Antibiotics profit from pH elevation to differing extents. The activities of amoxicillin and some macrolides are increased by one to two orders of magnitude [98, 99] offering a possible explanation of their increased efficacy in the presence of PPIs in vivo. However, the actual pH of the microenvironment where the bacterium colonizes the gastric epithelial surface is not known. Thus, definite proof is lacking that PPIs potentiate the effect of antibiotics by adjusting the pH appropriately for optimal activity of the antibiotic, and the relevance of pH-dependent inhibitory antimicrobial drug concentrations in vitro remains to be determined.

SUMMARY

PPIs have been established as the new “gold standard” for traditional acid-inhibitory treatment of the so called “peptic” diseases. Due to the high antisecretory and ulcer-healing potency of omeprazole, no major improvements of the efficacy in ulcer healing and pain relief can be expected. Pantoprazole, as a further development in PPIs, is characterized by improved pharmacokinetic behavior as well as by higher tissue selectivity and binding specificity and by a very low potential to interact with the cytochrome P450 enzyme system. These characteristics may provide the basis for low potential for side effects and for more favorable interaction profile, although the clinical relevance of these potential advantages remains to be proven. Reflux esophagitis will remain a domain for the traditional use of PPIs also in the future. However, in the treatment of gastroduodenal ulcers the acid inhibitory potential of PPIs will be used mainly to facilitate the eradication of *H. pylori*.

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