The Clinical Importance of Proton Pump Inhibitor Pharmacokinetics

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\textbf{Abstract}
Achieving the optimal clinical response for patients with upper gastrointestinal peptic disease is important. This response depends on the pathology treated as well as on the choice of proton pump inhibitor. Here, we identify factors in specific disease therapy and proton pump inhibitor (PPI) pharmacokinetic and pharmacodynamic characteristics that help us achieve this goal. These include differences in PPI bioavailability and acid-suppressive effects. Available data indicate that PPIs appear to have similar potency on a milligram basis, and that omeprazole and lansoprazole are more frequently double dosed than pantoprazole. The lower propensity for double dosing with pantoprazole may also result in lower medication acquisition costs and a reduction in physician visits due to ineffective therapy with the standard dosing of these other agents.

\section*{Introduction}
The widespread use and benefit of the proton pump inhibiting class of acid-suppressing drugs have been valuable tools in the treatment of a range of upper gastrointestinal diseases. This work will review the pharmacology of these agents to better understand their optimal dosing and dose intervals for clinical use. This review was written in the light of prescription audit data demonstrating that double dosing is more common with omeprazole than with pantoprazole. Here we review the known literature about specific upper gastrointestinal diseases. The pharmacokinetics of proton pump inhibitors (PPIs) have been summarized elsewhere \cite{1–6}, but a few issues are relevant to this discussion (table 1). First, there is a substantial difference in the bioavailability of these agents. Pantoprazole and lansoprazole have the highest extent of absorption. Pantoprazole has a bioavailability of 77\% after the first dose, and this does not change after repeated dosing \cite{10, 11}, while that of lansoprazole is 80\%. However, the bioavailability of omeprazole is 35\% after the first dose, and it increases to about 60\% with repeated doses \cite{12, 13}. This fact indicates that, based solely on the pharmacokinetics of these agents, it will take longer to reach the maximum therapeutic effect with omeprazole than with the other PPIs (except for esomeprazole – see below). The lower bioavailability of omeprazole, combined with a lower defined daily dose (DDD) (e.g., 20 mg for omepra-
Table 1. Differing pharmacokinetic parameters in PPIs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pantoprazole 40 mg</th>
<th>Omeprazole 20 mg</th>
<th>Lansoprazole 30 mg</th>
<th>Rabeprazole 20 mg</th>
<th>Esomeprazole 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability, %</td>
<td>77</td>
<td>30–40</td>
<td>80</td>
<td>52</td>
<td>64</td>
</tr>
<tr>
<td>Cmax, μmol/l</td>
<td>5.73</td>
<td>0.7</td>
<td>2.25</td>
<td>0.48</td>
<td>2.4</td>
</tr>
<tr>
<td>t1/2, h</td>
<td>1.2</td>
<td>0.7</td>
<td>1.2</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>AUC0–24, μmol·h/l</td>
<td>9.93</td>
<td>1.11</td>
<td>5.01</td>
<td>0.86</td>
<td>4.32</td>
</tr>
<tr>
<td>Linear pharmacokinetics</td>
<td>yes</td>
<td>no</td>
<td>yes (for oral doses of 15–60 mg)</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Factors that affect absorption</td>
<td>none</td>
<td>food</td>
<td>antacids</td>
<td>food</td>
<td>food</td>
</tr>
</tbody>
</table>

Compiled from following references: Product monographs for Pantoloc (or Protonix in US), Losec (or Prilosec in US), Prevacid, Aciphex (US), and Nexium, and Andersson et al. [7], Yasuda et al. [8] and Hassan-Alin et al. [9].

Pantoprazole vs. 40 mg for pantoprazole, will also result in lower serum concentrations than with pantoprazole. These lower serum concentrations may be one reason that explains the higher omeprazole doses required in some patients to treat acid-related diseases [14], a finding that has been observed in the treatment of patients with gastroesophageal reflux disease (GERD) [15].

Another omeprazole formulation, a multiple-unit pellet system (MUPS), is also available in many countries. The highly variable bioavailability has also been demonstrated in this new formulation [16], which indicates that it was not solely a feature of the previously available encapsulated enteric-coated granule formulation, but a feature inherent in omeprazole as a molecule. This finding is also consistent with the 40-mg standard dose selected for the recently approved single isomer of omeprazole, esomeprazole. As is the case with omeprazole, esomeprazole bioavailability increases with the duration of administration, which may cause esomeprazole to take longer than other PPIs to reach its maximum effect, as identified by Hassan-Alin et al. [9].

Another important difference between these agents is the interindividual variability observed in their pharmacokinetic parameters. Area under the curve (AUC) is a good example, because it has been demonstrated to correlate with the degree of acid suppression [16,17], which is known to correlate with cure of acid-related diseases [14,17,18]. The coefficient of variation (CV) is a relative measure that describes the variation of a variable around its mean. The CVs for omeprazole and pantoprazole AUC were pooled from available pharmacokinetic studies to gain insight into potential interindividual variability differences between these agents [19–24]. The descriptive analysis of these data demonstrates that pantoprazole displays a less pronounced interindividual variability than omeprazole. The CV medians and ranges are shown in figure 1. On day 1 of dosing, omeprazole displays almost 1.5 times the variability of pantoprazole, and this difference is even greater (over 2.2 times) on day 7. Interindividual variability in pharmacokinetic parameters is an important issue to consider when selecting therapy, because it has been proven to have a significant impact on acid suppression [15], cure rates of *Helicobacter pylori* [18], and adverse effects [23,25].

The variable omeprazole and esomeprazole bioavailability is indicative of nonlinear pharmacokinetics. When the dose of a drug with linear pharmacokinetics (e.g., pantoprazole, lansoprazole, rabeprazole) is doubled, the serum concentration also doubles. However, doubling the dose of a drug with nonlinear pharmacokinetics (e.g., omeprazole) will result in serum concentrations that will be lesser or greater than the expected doubling. In other words, serum concentrations do not increase in direct proportion to a dose increase. One potential reason for this demonstrated characteristic of omeprazole and esomeprazole is that the intestinal metabolism may become saturated over time, which then results in increased serum concentrations [13,26,27]. These characteristics are advantages for pantoprazole, as pantoprazole has greater predictability, which translates into superior acid control at its usual dose compared with omeprazole.

Studies have shown that pantoprazole and omeprazole are equipotent on a milligram per milligram basis [28,29]. The pharmacodynamic data from these studies indi-
cate that the usual defined daily dose of pantoprazole, 40 mg, is a better alternative for acid suppression than the usual 20-mg dose of omeprazole. One of these studies also evaluated lansoprazole 30 mg, and found it to have acid-suppressive effects that were comparable to those of pantoprazole 40 mg [29]. This difference in tablet strength may be one reason why the pH effects of pantoprazole 40 mg and omeprazole 20 mg demonstrated the superiority of the pantoprazole regimen [28, 29]. Also of relevance are two other studies that compared pantoprazole 40 mg with omeprazole 40 mg, and found that there was no significant difference in 24-hour intragastric pH values between groups [29, 30].

Another recent randomized study was conducted in 14 healthy H. pylori-negative male volunteers, comparing the effect of pantoprazole 40 mg and omeprazole 20 mg on meal-stimulated acid secretion [31]. During the first 3 days of dosing, pantoprazole 40 mg demonstrated a significantly faster onset of action and higher antisecretory potency than omeprazole 20 mg [31]. From these data, it appears that pantoprazole acts more rapidly and has a more pronounced acid-suppressive effect than omeprazole when they are given at their usual recommended oral doses.

Pantoprazole 40 mg was also compared with esomeprazole 40 mg in 48 patients with symptomatic GERD [32]. The duration of intraesophageal pH < 4 over 24 h was not significantly different between pantoprazole and esomeprazole, being decreased by 18.7 and 19.2%, respectively.

Several studies have also reported the acid-suppressive effects of the other PPIs. Lansoprazole 30 mg has been compared with omeprazole 20 and 40 mg [33–36]. Although results have varied to some extent, the trend has been for equivalent milligram potencies between these agents, with lansoprazole 30 mg proving more potent than or equivalent to omeprazole 20 mg, but less than omeprazole 40 mg [33, 36]. Interestingly, the observed intersubject variation in intraesophageal pH was high at 30% for both lansoprazole and omeprazole [33]. Lansoprazole does, however, appear to have a more rapid onset of action than omeprazole when tested in healthy volunteers [37].

Katashima et al. [38] developed a pharmacokinetic/pharmacodynamic model to describe the relationship between PPI plasma concentration and acid-suppressive effects. When the model was calculated with clinical pharmacokinetic and pharmacodynamic data, the longest half-life of acid suppression was identified in pantoprazole, at < 45.9 h, compared with < 27.5 h for omeprazole and < 12.9 h for lansoprazole. This may indicate stronger binding of pantoprazole to the proton pump. The longer duration of acid suppression for pantoprazole results in a lower likelihood that patients will experience breakthrough nighttime symptoms and require an additional dose before the end of the dosing interval. Differing serum half-lives and the capacity to bind proton pumps may also partially explain these clinical observations.

Data are also available on the other two PPIs: rabeprazole and esomeprazole. The acid-suppressive efficacy of rabeprazole 20 mg has been shown to be similar to that of omeprazole 20 mg [6, 39]. As is the case with omeprazole and esomeprazole [40], the acid-suppressive effect of rabeprazole increases over 7 days of dosing [41]. The acid-suppressive effect of esomeprazole 20 mg also appears to be similar to that of omeprazole 20 mg, while increasing the esomeprazole dose to 40 mg improves the effect [42]. This suggests that any clinical improvement noted on esomeprazole is more likely due to the dose increase than to any molecular advantage.

**Clinical Response Data**

DDD is a unit that represents 'the assumed average maintenance dose per day for a drug used for its main indication in adults.' For example, the DDDs for omeprazole and pantoprazole are 20 and 40 mg, respectively. A prescribed daily dose (PDD) that is higher than the DDD may indicate that the higher dose is required to elicit a response in many patients. Table 2 presents the amount of a particular dosage form used (e.g., 20 or 40 mg tablet) for omeprazole, lansoprazole, and pantoprazole.
Table 2. Country-specific dosing for omeprazole and pantoprazole from January to December 2000

<table>
<thead>
<tr>
<th>Country</th>
<th>Pantoprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg</td>
<td>40 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Germany</td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Australia</td>
<td>1.0</td>
<td>1.1–2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Brazil</td>
<td>1.1–1.2</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Canada</td>
<td>not marketed</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>United States of America</td>
<td>not available</td>
<td>1.0</td>
<td>1.3</td>
</tr>
</tbody>
</table>

ample, 1.0 would indicate that all (i.e., 100%) of the omeprazole 20 mg tablets are used as single doses, whereas 1.2 would indicate that the average dosing of the 20-mg tablets is 20% higher (i.e., 24 mg in this case). These data indicate that the range of dosing for the 40-mg omeprazole tablets is closer to that observed with pantoprazole 40 mg and lansoprazole 30 mg. This less frequent need for higher dosing with omeprazole 40 mg compared with omeprazole 20 mg would therefore indicate that a 20-mg dose is not optimal, and it further supports the claim that these drugs have similar milligram potencies [6]. In countries where a 40-mg formulation is not available (e.g., Australia and Canada), substantially more 20-mg tablets are dosed higher than in countries where the 40-mg formulation is available. The frequency of double dosing required with the DDD of pantoprazole (i.e., 40 mg) and lansoprazole (i.e., 30 mg) is consistently lower than that observed with the DDD of omeprazole (i.e., 20 mg). These data indicate that 40 mg may be the ideal dose for all PPIs.

Further evidence regarding this issue has recently been published [43]. Despite the fact that published literature did not reveal substantial differences between proton pump inhibitors, an audit of lansoprazole use after the substitution revealed that as many as 25% of patients required a double dose (i.e., 60 mg daily) of lansoprazole. Interestingly, this figure was 17% for omeprazole. The potential for double dosing may therefore also be an important consideration with this PPI.

Canadian prescription claim data also support these observations and allow for the exclusion of potentially confounding factors. Data on prescription claims from August 1998 to July 2000 indicate that, compared with pantoprazole, almost 3 times the number of omeprazole and 1.5 times the number of lansoprazole claims were for double doses (fig. 2). These numbers remained consistent when different time periods were evaluated. Of the patients who were double dosed with a PPI, approximately the same number of patients receiving omeprazole and pantoprazole (i.e., 8.3 and 7.0%, respectively) were being treated for H. pylori. Double dose is defined as double dose PPI in combination with two antibiotics dispensed on the same day (data quoted with permission by Brogan Inc., Ottawa, Canada). Therefore, even when potential confounders are considered, omeprazole and lansoprazole are double dosed more frequently than pantoprazole.

Figure 3 illustrates the increase in omeprazole dose requirements over 10 years of follow-up, as well as the increase in the percentage of patients who required more than 40 mg of omeprazole for symptomatic control over 10 years, with a peak of about 24% at the end of the follow-up period [45, 46]. Although these patients had severe H2 receptor antagonist (H2RA)-resistant esophagitis, and follow-up data over such a time frame are not available for the other PPIs, the percentage of patients on double doses in this study is consistent with that presented in the prescription audit data above (i.e., 20.5%), a fact that lends further support to the figures [47–49].

Despite the fact that data from everyday practice demonstrate that double doses of omeprazole and lansoprazole are used more commonly than double doses of pantoprazole, many published clinical studies have not shown significant differences between omeprazole 20 mg and pantoprazole 40 mg in duodenal ulcers (DU), gastric ulcers (GU), and GERD [50–52]. Three potential reasons were identified that may explain why the clinical study results are different from the observations in the clinical practice setting (derived from the prescription audit data).
First, patients seek care from their physicians because of their symptoms, whereas most GERD clinical studies to date have focused on endoscopic endpoints rather than symptomatic relief.

Second, the strict criteria used in designing and conducting clinical trials are such that extrapolation of their results to usual clinical practice is not typically appropriate. All patients present to a physician because of specific complaints. If heartburn is a major or the sole symptom, GERD is the cause in about 75% of patients [53]. Patients with endoscopy-negative disease make up the majority of cases, but to date, studies have focused on healing esophagitis [53]. Symptoms were most often included as secondary endpoints, hence the trials were not specifically designed to address the issue of symptom relief. The trend is now for more studies to focus on the symptoms of the patients rather than solely on endoscopic endpoints [53–55]. For example, the symptom relief rates at day 3 were significantly higher with pantoprazole 20 mg than with omeprazole MUPS 10 mg (31 vs. 19%, respectively, p < 0.001) – an important finding, given the fact that rapid symptom relief is essential to patients presenting with heartburn. By the 2-week point, the benefit of pantoprazole (i.e., 68 vs. 58%) was no longer statistically significant (p = 0.07). In addition, Scholten et al. [56] demonstrated that after 2 days of therapy, pantoprazole 40 mg provided symptom relief that was equivalent to that obtained with 4 days of therapy with omeprazole MUPS 20 mg. This is especially important given the fact that 80% of patients take their medications only when symptoms are a problem, and they need prompt acute relief from their heartburn [57]. It is therefore possible that patients who receive omeprazole experience suboptimal symptom relief early in therapy, due to the drug’s slow onset of action. Possibly, these individuals then return to the physician, who prescribes higher omeprazole doses. Both the physician visits and the higher omeprazole doses result in higher costs to the health care system.

Third, it is becoming evident that the symptoms that had been the focus of the research may not be the ones that are clinically most relevant for GERD. Traditionally, the symptoms of heartburn – acid regurgitation and pain on swallowing – were assessed. However, it is now apparent that the symptoms of heartburn and acid regurgitation universally represent GERD and are clinically most relevant [58]. It is also known that the term ‘heartburn’ can be interpreted unreliably by patients [53].

Clinical trials also have various restrictions or limitations inherent in their design that make extrapolation to the usual clinical practice setting difficult and may provide explanations for the observed differences between practice and clinical trial data. Only specific patients are...
included in clinical trials (e.g., grade II–III Savary-Miller reflex esophagitis patients), and their assigned therapy is prescribed in a predetermined method (e.g., omeprazole 20 mg once daily in the morning for 4 weeks, followed by 4 weeks of 40 mg in patients who are not healed). Patients in practice settings do not necessarily fall within these strict inclusion criteria; they represent a much broader patient population. Their compliance with drug regimens is also monitored less closely and likely to be different from that of patients in clinical studies. These strict methodological requirements of clinical trials may account, at least in part, for some of the observed differences between practice data and clinical trial data. This is further supported by a recent article that reports on the long-term use of omeprazole in reflux esophagitis patients [45]. The article supports the fact that doses greater than 20 mg are required in many patients to achieve adequate symptom control.

Prescription audit and usage data provide insight into the total population receiving PPIs. As outlined above, patients included in clinical trials are selected according to specific inclusion criteria, and are not representative of the population as a whole. The patients included in the prescription audit data represent a much broader range, including those with comorbidities (e.g., history of bleeding ulcer or hepatic impairment) and those receiving concomitant medications (e.g., NSAIDs, H₂RAs, or antacids). Some of these factors may contribute to the observed PDD/DDD differences between pantoprazole and omeprazole.

Patients in clinical trials also take their drug exactly as prescribed for the duration of the trial. This is especially evident when per-protocol analyses are reported, which only account for patients who completed the treatment as specified in the study methodology, and exclude patients who deviated from the protocol. Intention-to-treat analyses are more conservative in their efficacy estimate, but they maintain the effect of randomization and compensate to some degree for the ‘real-life’ problems, such as noncompliance with treatment [47]. Compliance studies from practice settings have demonstrated that 80% of patients receiving long-term PPIs use these agents only when their symptoms are problematic [57]. Although no data exist demonstrating whether or not this is also the case with short-term use, it is a possibility that cannot be ignored. If this is indeed the case, sporadic use (e.g., on-demand treatment or noncompliance) of omeprazole or esomeprazole would potentially result in subtherapeutic serum concentrations as their low initial bioavailability reaches its maximum only after a few days. This would not be a problem with pantoprazole, however, which displays a high bioavailability of 77% with the first dose that is maintained throughout therapy. Its faster symptom relief is also an asset in such situations [18]. The higher and more predictable bioavailability observed with lansoprazole and rabeprazole also make such problems less likely.

When physicians are treating patients who are included in a clinical study, they are somewhat restricted in terms of treatment options. They must follow the treatment algorithm outlined by the clinical trial protocol, unless the patient is withdrawn from the study. Physicians in clinical practice are free to treat patients as they see fit, and many choose to use 40 mg of omeprazole instead of the recommended 20-mg dose, or 60 mg of lansoprazole instead of 30 mg, probably because their experience with the agent justifies using the higher dose [43]. No published data are available to provide insight into the reasons for these treatment decisions, but these observations could not be derived from well-designed clinical trials with strict treatment algorithms.

**Duodenal Ulcer**

Acid suppression is essential to heal peptic ulcer disease. It has been established that any acid-suppressive regimen that maintains gastric pH above 3.0 for 18–20 h a day will heal 100% of duodenal ulcers in 4 weeks [15]. It was also concluded in this study that a longer duration of antisecretory effect and/or a longer duration of therapy are of greater importance than drug potency for duodenal ulcer healing. How these observations are related to *H. pylori* is currently unknown, but the principle is probably still applicable. The more so as slow metabolizers of omeprazole, who are subjected to higher serum concentrations and demonstrate greater acid suppression, achieve higher cure rates than rapid metabolizers who receive the same eradication regimen [59]. Furthermore, while not part of the model of Burget et al. [60], it is likely that most of the subjects were *H. pylori* positive, given that they had a DU.

Using 40 mg of omeprazole has been found to provide higher cure rates for DU compared with the use of 20 mg. Lauritsen et al. [61] conducted a double-blind trial in over 1,000 patients and demonstrated that the cure rates for DUs with omeprazole 40 mg were significantly superior to those of omeprazole 20 mg. After 2, 4, and 6 weeks of therapy, the healing rates were 71.6%, 97.1% and 99.8%, respectively, for the 40-mg dose, and 66.0%, 93.3 and
96.7% for the 20-mg dose [61]. The differences between doses were significant at all time periods, using both intention-to-treat and per-protocol analyses. Beker et al. [62] compared the efficacy of omeprazole 20 mg with pantoprazole 40 mg in patients with DU. The 2- and 4-week healing rates for omeprazole were 65 and 89%, respectively, while those of pantoprazole were 71 and 96%. Although these differences did not reach statistical significance, the efficacy results demonstrate a trend for superior healing rates with pantoprazole 40 mg [62]. In addition, a dose-response study demonstrated that increasing the dose of pantoprazole beyond 40 mg provided no additional benefit [61].

The other PPIs have also been studied in this setting. Studies have shown that lansoprazole 30 mg and omeprazole 20 mg have similar efficacy [63], while other trials have shown similar efficacy between lansoprazole 30 mg and omeprazole 40 mg [64]. Rabeprazole 20 mg has also been compared with omeprazole 20 mg in this setting. There was no significant difference in healing between the two agents, but symptom relief was superior with rabeprazole [65]. No studies of esomeprazole are available in this setting. The overall conclusion of these trials is that a 40-mg dose appears to be optimal for all PPIs.

**Gastric Ulcer**

When discussing GUs, a meta-analysis from 1991 reported that maintaining intragastric pH above 3.0 for 18 h a day should heal 100% of GUs within 8 weeks [60]. A significant correlation between suppression of 24-hour intragastric acid secretion and GU healing rates was demonstrated after 2, 4, and 8 weeks, with the highest rates provided by PPIs [18]. As long-term (i.e., 8 weeks) acid suppression with any agent is likely to result in GU cure [60], relevant differences between agents are more likely to be identified in the shorter-term follow-up periods (i.e., 2 and 4 weeks).

Walan et al. [66] compared omeprazole 20 and 40 mg with ranitidine 150 mg twice daily in healing benign gastric ulcers. Both omeprazole regimens were superior to ranitidine. Healing rates for omeprazole at 4 and 8 weeks were 69 and 80%, respectively, for the 20-mg dose, and 89 and 96% for the 40-mg dose. This difference was significant at the 8-week point, again demonstrating the superiority of the 40-mg dose. These findings were confirmed in a subsequent placebo-controlled study that compared 20- and 40-mg omeprazole doses [66]. Interestingly, the omeprazole prescribing information from the United States recommends an initial dose of 40 mg for the treatment of benign GU [18].

While the treatment of both DU and GU with acid suppression alone may only be relevant for a small percentage of patients today (because of the important role of \textit{H. pylori} in ulcer pathogenesis), the usual dose of pantoprazole is more effective than that of omeprazole when assessment is made at 4 weeks [68]. A randomized study in 219 patients with gastric ulcers compared pantoprazole 40 mg with omeprazole 20 mg daily [68]. After 4 weeks of therapy, significantly more pantoprazole-treated patients were healed [68]. This is not surprising, given the fact that a longer duration of therapy is expected to improve outcomes, even with H2RAs. Although further studies are required to confirm these findings, this study suggests that pantoprazole may heal gastric ulcers faster than omeprazole. A trend for superior symptom relief with pantoprazole was also noted, with 79% of patients being symptom free at 2 weeks compared with 68% taking omeprazole [68].

Lansoprazole 30 mg and rabeprazole 20 mg are both as effective as omeprazole 20 mg in healing gastric ulcers, but provide superior symptomatic relief [63, 69]. No studies of esomeprazole are available in this setting.

**Gastroesophageal Reflux Disease**

New practice guidelines for the treatment of GERD recommend the use of PPIs, stating that they provide 'rapid symptomatic relief and healing of esophagitis in the highest percentage of patients' [63]. When treating reflux esophagitis, it has been demonstrated that the degree and duration of acid suppression over a 24-hour period are the major determinants of healing after 8 weeks of therapy [70]. It is, therefore, not surprising that PPIs are more effective than H2RAs in treating this condition.

As was the case with DU and GU, a 40-mg omeprazole dose is also more effective than a 20-mg one in the treatment of reflux esophagitis. One study demonstrated that, after 4 weeks of omeprazole 20 mg had been unsuccessful in healing esophagitis, 4 subsequent weeks of 40 mg were significantly better than 20 mg [71]. Two other studies found that omeprazole 40 mg was superior to 20 mg in the acute healing of reflux esophagitis [72, 73]. Dent [26] demonstrated the superiority of 40 mg of omeprazole over 20 mg in healing esophagitis after 4 weeks of therapy, but the difference (85 for 40 vs. 79% for 20 mg) was no longer statistically significant after 8 weeks of therapy. The prescribing information for omeprazole in various countries...
is consistent with these findings in their recommendations to increase the dose to 40 mg in patients who fail on 20 mg [74, 75]. A recent consensus statement from Yale University on the treatment of GERD also states that symptom relief may not be adequate with 20 mg of omeprazole, and that ‘the dose of this drug might need to be increased to 20 mg b.i.d. or even more to achieve optimal results’ [76]. On the other hand, increasing the pantoprazole dose to 80 mg provides no additional benefit over the usual 40-mg dose in the majority of patients, even after 8 weeks of therapy [74], and the prescribing information is consistent with these findings [77].

The results of published meta-analyses assessing PPIs in the treatment of reflux esophagitis confirm that they are clearly superior to H2RAs in terms of rapidity and extent of symptomatic relief and healing, regardless of endoscopic grade [50–52, 77, 78]. In this meta-analysis of over 1,400 patients with grade II to IV reflux esophagitis, pantoprazole 40 mg produces superior 4-week and 8-week healing rates compared with omeprazole 20 mg, probably due to the larger sample size provided by this analysis. Four-week healing rates were 73% for pantoprazole 40 mg and 60% for omeprazole 20 mg, while these figures increased to 88 and 79% at 8 weeks for each drug, respectively (sub-analysis of published meta-analysis by Chiba [78], on file at Byk Gulden) (table 3). This significant difference was also observed for 2- and 4-week symptom relief rates.

Recent studies that were not included in the meta-analysis also support the superior efficacy of pantoprazole at its usual dose. One such study compared omeprazole 20 mg with pantoprazole 40 mg in the treatment of grade II–III reflux esophagitis [50]. In this trial, pantoprazole 40 mg healed reflux esophagitis in 86.8% of patients after 4 weeks, compared with 82.5% of omeprazole 20 mg-treated patients [50]. Although the difference was not statistically significant, it demonstrates a superiority trend for pantoprazole. In elderly patients with symptomatic grade I–III esophagitis, pantoprazole 40 mg was also more effective than omeprazole 20 mg at healing esophagitis after 8 weeks of therapy [51]. Patients with severe heartburn may have more rapid symptom relief with pantoprazole 40 mg compared with omeprazole MUPS 20 mg [56] (fig. 4). Another study comparing omeprazole 20 mg with pantoprazole 20 mg in healing grade I reflux esophagitis showed no significant difference between these regimens [79]. In addition, when pantoprazole 40 mg and omeprazole 40 mg are compared in patients with grade II–III reflux esophagitis, no difference in healing rates is observed after 4 and 8 weeks of therapy [80]. These results provide further support for pantoprazole 40 mg as the optimal drug and dose combination.

Recently, a placebo-controlled, randomized, double-blind, multi-center study of pantoprazole 10, 20, and 40 mg demonstrated that 4-week healing rates achieved with pantoprazole 40 mg (86%) were similar to those achieved after 8 weeks of therapy with pantoprazole 20 mg (90%) in patients with grade II esophagitis [81]. Better 24-hour pH control was accomplished in patients treated with omeprazole and the addition of a bedtime H2RA to control nighttime acid [82]. In addition, Bardhan and van Rensburg [83] compared the symptom relief and healing efficacies of omeprazole 20 mg with that of pantoprazole 20 mg in 328 patients with grade I esophagitis. After 4 and 8 weeks of therapy, both drugs achieved comparatively high symptom relief and healing rates in these patients, supporting the lack of clinically significant difference between these two doses.

Pantoprazole 40 mg was also compared with esomeprazole 40 mg in randomized double-blind studies of patients with moderate to severe GERD. Daytime and nighttime symptom relief at 4 weeks was similar in both groups of the first study [84], and healing was around 90% for both groups over the 8-week study [85].

Data are also available for the other PPIs. Lansoprazole 30 mg was compared with pantoprazole 40 mg in 561 patients with grade II-III reflux esophagitis [86]. Healing rates were around 80% for both groups after 4 weeks of therapy. After 8 weeks, there was a trend for superiority of pantoprazole over lansoprazole with 90 and 86% healing

### Table 3. Results of meta-analysis of over 1,400 patients with grade II–IV reflux esophagitis

<table>
<thead>
<tr>
<th></th>
<th>Healing rates, %</th>
<th>Symptom relief rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>60 (57–63)</td>
<td>79 (76–82)</td>
</tr>
<tr>
<td>Pantoprazole 40 mg</td>
<td>73 (69–78)</td>
<td>88 (85–91)</td>
</tr>
</tbody>
</table>

* p < 0.025. Figures in parentheses are 95% CI.
Clinical Importance of Proton Pump Inhibitor Pharmacokinetics

Cost Implications of Dosing Regimens

There are several cost implications of the PDD-DDD data presented above. These include the frequency of double dosing, compliance with the prescribed regimen, and the frequency of physician visits. Maximizing the therapeutic benefit of any prescribed drug regime could result in cost savings to the health system and provide a basis for cost-effective formulary decision making.

Although the use of PPIs as first-line therapy for GERD is not common practice – despite recent guidelines advocating such use – recent evidence indicates that these agents are more cost effective than H2RAs [91]. Physicians will probably still want access to an H2RA for use in many patients; however, they will also require a PPI, especially in the acute care setting where many in-patients will need to continue on the drugs they received as out-patients. Physicians will also need an H2RA for those patients who require acid suppression for more acute acid-related pathology. It has been suggested that the dictating factor in PPI selection should be cost alone [92]. Consequently, other factors should be considered in selecting a PPI for inclusion on a formulary. Such factors must include efficacy, predictability, cost-effectiveness, propensity for drug interactions, and formulation availability. Based on the data presented in this review, pantoprazole is at least as effective as the other PPIs in the treatment of the various acid-related conditions. In addition, it is available as an intravenous formulation and has no known metabolic drug interactions [6, 93]. These factors combined with Pantoprazole’s rapid onset and sustained action may be taken into consideration when deciding on which PPI to include in formularies.

Conclusion

The PPI class of substituted benzimidazoles as a group offers a major step forward in the management of upper gastrointestinal symptoms as well as acute gastrointestinal bleeding compared to the H2RAs [53]. These agents are widely accepted drugs in the clinical management of upper gastrointestinal disease. Prescription audit data indicate that omeprazole and lansoprazole are more frequently double dosed than pantoprazole. Although these agents appear to have equivalent acid-suppressing capabilities on a milligram per milligram basis, our understanding of their collective mechanisms of action should help ensuring their efficacy and reducing recidivism.

Acknowledgement

This paper is dedicated to the memory of Scott Paget. B.R. Yacyshyn and A.B.R. Thomson are on the Speaker’s Bureau of ALTANA, Inc.
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