Review

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The Clinical Importance of Proton Pump Inhibitor Pharmacokinetics

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Proton pump inhibitors · Gastric ulcer · Duodenal ulcer · Reflux disease

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.

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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 [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 [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 [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-

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Table 1. Differing pharmacokinetic parameters in PPIs

Parameter	Pantoprazole 40 mg	Omeprazole 20 mg	Lansoprazole 30 mg	Rabeprazole 20 mg	Esomeprazole 40 mg
Bioavailability, %	77	30–40	80	52	64
C _{max} , µmol/l	5.73	0.7	2.25	0.48	2.4
t _{1/2} , h	1.2	0.7	1.2	1.0	0.9
AUC _{0–24} , µmol • h/l	9.93	1.11	5.01	0.86	4.32
Linear pharmacokinetics	yes	no	yes (for oral doses of 15–60 mg)	yes (for oral doses of 10–40 mg)	no
Factors that affect absorption	none	food	antacids food	food not studied	food

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].

zole 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 dif-

ferences 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

Fig. 1. Median and range for CV values for omeprazole and pantoprazole AUC data on day 1 and day 7 of dosing.

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. For ex-

Table 2. Country-specific dosing for omeprazole and pantoprazole from January to December 2000

Country	Pantoprazole		Lansoprazole		Omeprazole	
	20 mg	40 mg	15 mg	30 mg	20 mg	40 mg
Germany	1.1	1.2	1.2	1.1	1.2–1.3	1.1–1.3
Australia	1.0	1.1–2.0	1.0	1.1	1.2–1.4	not available
Brazil	1.1–1.2	1.1	1.2	1.1	1.1	1.0–1.2
Canada	not marketed	1.1	1.1	1.1	1.2–1.6	not available
United Kingdom	1.0	1.0	1.0	1.0	1.1	1.1
United States of America	not available	1.0	1.3	1.2	1.2	1.1

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).

Fig. 2. Vertical axis represents improvement of reflux symptoms (score points) showing that pantoprazole delivers a level of symptomatic relief in 2 days that omeprazole delivers in 4 days.

Fig. 3. Comparison of mean omeprazole dose and percent of patients requiring more than 40 mg daily to control erosive esophagitis. Figure reproduced from Armstrong [44].

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 reflux 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 *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

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

	Healing rates, %		Symptom relief rates	
	4 weeks	8 weeks	2 weeks	4 weeks
Omeprazole 20 mg	60 (57–63)	79 (76–82)	60 (55–65)	72 (69–75)
Pantoprazole 40 mg	73 (69–78)*	88 (85–91)*	71 (67–76)*	88 (84–91)*

* $p < 0.025$. Figures in parentheses are 95% CI.

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

Fig. 4. Percentage of claims that are for double doses of the 3 PPIs available in Canada in 2000. Canadian claims for these agents were compiled over an 18-month period up to, and including, July 2000.

rates, respectively. A recent meta-analysis demonstrated that lansoprazole 30 mg is significantly faster than omeprazole 20 mg in healing reflux esophagitis [63, 87]. Rabeprazole 20 mg is as effective as omeprazole 20 mg in healing and preventing recurrence of erosive esophagitis, but may provide more rapid symptom relief [6]. Esomeprazole 40 mg has been found to be significantly more effective than omeprazole 20 mg at healing and relieving symptoms of reflux esophagitis [88, 89]. In one study, healing rates for esomeprazole 40 mg and omeprazole 20 mg were 94 and 87%, respectively [88]. Although this effect was statistically significant, its clinical significance is unclear. The superiority of esomeprazole is probably related to the higher dose rather than to clinically significant improvements of the *S*-isomer over the drug administered as a racemic mixture. These data all appear to support the fact that PPIs (including esomeprazole) probably have similar milligram potencies in the treatment of GERD [90].

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]. Physi-

cians 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 in combination 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.

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References

- Fitton A, Wiseman L: Pantoprazole. A review of its pharmacological properties and therapeutic use in acid-related disorders. *Drugs* 1996;51:460-482.
- Benet LZ, Zech K: Pharmacokinetics – a relevant factor for the choice of a drug? *Aliment Pharmacol Ther* 1994;8(suppl 1):25-32.
- Clissold SP, Campoli-Richards DM: Omeprazole. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. *Drugs* 1986;32:15-47 [published erratum appears in *Drugs* 1986;32:preceding 383].
- Wilde MI, McTavish D: Omeprazole. An update of its pharmacology and therapeutic use in acid-related disorders. *Drugs* 1994;48:91-132.
- McTavish D, Buckley MM, Heel RC: Omeprazole. An updated review of its pharmacology and therapeutic use in acid-related disorders. *Drugs* 1991;42:138-170.
- Stedman CAM, Barclay ML: Review article: Comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *Aliment Pharmacol Ther* 2000;14:963-978.
- Andersson T, Holmberg J, Rohss K, et al: Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. *Br J Clin Pharmacol* 1998;45:369-375.
- Yasuda S, Ohnishi A, Ogawa T, et al: Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. *Int J Clin Pharmacol Ther* 1994;32:466-473.
- Hassan-Alin M, Andersson T, Bredberg E, Rohss K: Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. *Eur J Clin Pharmacol* 2000;56:665-670.
- Huber R, Hartmann M, Bliesath H, Luhmann R, Steinijans VW, Zech K: Pharmacokinetics of pantoprazole in man. *Int J Clin Pharmacol Ther* 1996;34(suppl 1):S7-S16.
- Pue MA, Laroche J, Meineke I, De Mey C: Pharmacokinetics of pantoprazole following single intravenous and oral administration to healthy male subjects. *Eur J Clin Pharmacol* 1993;44:575-578.
- Cederberg C, Andersson T, Skanberg I: Omeprazole: Pharmacokinetics and metabolism in man. *Scand J Gastroenterol Suppl* 1989;166:33-40.
- Andersson T, Cederberg C, Heggelund A: The pharmacokinetics of single and repeated once-daily doses of 10, 20 and 40 mg omeprazole as enteric-coated granules. *Drug Invest* 1991;3:45-52.
- Mohamed AH, Hunt RH: The rationale of acid suppression in the treatment of acid-related disease. *Aliment Pharmacol Ther* 1994;8(suppl 1):3-10.
- Burget DW, Chiverton SG, Hunt RH: Is there an optimal degree of acid suppression for healing of duodenal ulcers? A model of the relationship between ulcer healing and acid suppression. *Gastroenterology* 1990;99:345-351.
- Ehrlich A, Lucker PW, Wiedemann A, Sander P, Huber R, Mascher H: Comparison of the pharmacodynamics and pharmacokinetics of pantoprazole (40 mg) as compared to omeprazole MUPS (20 mg) after repeated oral dose administration. *Methods Find Exp Clin Pharmacol* 1999;21:47-51.
- Londong W, Londong V, Cederberg C, Steffen H: Dose-response study of omeprazole on meal-stimulated gastric acid secretion and gastrin release. *Gastroenterology* 1983;85:1373-1378.
- Howden CW, Hunt RH: The relationship between suppression of acidity and gastric ulcer healing rates. *Aliment Pharmacol Ther* 1990;4:25-33.
- Tolman KG, Sanders SW, Buchi KN, Karol MD, Jennings DE, Ringham GL: The effects of oral doses of lansoprazole and omeprazole on gastric pH. *J Clin Gastroenterol* 1997;24:65-70.
- Tanaka M, Ohkubo T, Otani K, Suzuki A, Kaneko S, Sugawara K, et al: Metabolic disposition of pantoprazole, a proton pump inhibitor, in relation to S-mephenytoin 4'-hydroxylation phenotype and genotype. *Clin Pharmacol Ther* 1997;62:619-628.
- Jansen JB, Lundborg P, Baak LC, Greve J, Ohman M, Stover C, et al: Effect of single and repeated intravenous doses of omeprazole on pentagastrin stimulated gastric acid secretion and pharmacokinetics in man. *Gut* 1988;29:75-80.
- Pue MA, Laroche J, Meineke I, De Mey C: Pharmacokinetics of pantoprazole following single intravenous and oral administration to healthy male subjects. *Eur J Clin Pharmacol* 1993;44:575-578.
- Furuta T, Ohashi K, Kosuge K, Zhao XJ, Takashima M, Kimura M, et al: CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. *Clin Pharmacol Ther* 1999;65:552-561.
- Chang M, Tybring G, Dahl ML, Gotharson E, Sagar M, Seensalu R, et al: Interphenotype differences in disposition and effect on gastrin levels of omeprazole – suitability of omeprazole as a probe for CYP2C19. *Br J Clin Pharmacol* 1995;39:511-518.
- Sagar M, Janczewska I, Ljungdahl A, Bertilsson L, Seensalu R: Effect of CYP2C19 polymorphism on serum levels of vitamin B₁₂ in patients on long-term omeprazole treatment. *Aliment Pharmacol Ther* 1999;13:453-458.
- Dent J: Australian clinical trials of omeprazole in the management of reflux oesophagitis. *Digestion* 1990;47(suppl 1):69-71.
- Astra: Losec capsules 10/20/40 mg. Prescribing Information 1998; United Kingdom.
- Hartmann M, Theiss U, Huber R, Luhmann R, Bliesath H, Wurst W, Lucker PW: Twenty-four hour intragastric pH profiles and pharmacokinetics following single and repeated oral administration of the proton pump inhibitor pantoprazole in comparison to omeprazole. *Aliment Pharmacol Ther* 1996;10:359-366.
- Scholtz H: Comparison of the effects of lansoprazole, omeprazole and pantoprazole on 24-hour gastric pH in healthy males. *S Afr Med J* 1995;85:915.
- Koop H, Kuly S, Flug M, Schneider A, Rose K: Comparison of 24-h intragastric pH and 24-hour gastrin profiles during therapy with the proton pump inhibitors pantoprazole and omeprazole (abstract). *Gut* 1994;35(suppl 4):A79 (No 1172).
- Dammann HG, Burkhardt F: Pantoprazole versus omeprazole: Influence on meal-stimulated gastric acid secretion. *Eur J Gastroenterol Hepatol* 1999;11:1277-1282.
- Simon B, Mueller P, Gatz G, Sander P: Equivalent effect of pantoprazole 40 mg and esomeprazole 40 mg o.d. on intra-esophageal pH in patients with symptomatic GERD. *Am J Gastroenterol* 2001;96(suppl 9):108.
- Katz PO, Xue S, Castell DO: Control of intragastric pH with omeprazole 20 mg, omeprazole 40 mg, and lansoprazole 30 mg. *Aliment Pharmacol Ther* 2001;15:647-652.
- Frazzoni M, De Micheli E, Grisendi A, Savarino V: Lansoprazole vs. omeprazole for gastro-oesophageal reflux disease: A pH-metric comparison. *Aliment Pharmacol Ther* 2002;16:35-39.
- Langtry HD, Wilde MI: Lansoprazole: An update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. *Drugs* 1997;54:473-500.
- Frazzoni M, De Micheli E, Grisendi A, Savarino V: Lansoprazole vs. omeprazole for gastro-oesophageal reflux disease: A pH-metric comparison. *Aliment Pharmacol Ther* 2002;16:35-39.
- Thoring M, Hedenström H, Eriksson LS: Rapid effect of lansoprazole on intragastric pH: A crossover comparison. *Scand J Gastroenterol* 1999;34:341-345.
- Katashima M, Yamamoto K, Tokuma Y, Hata T, Sawada Y, Iga T: Comparative pharmacokinetic/pharmacodynamic analysis of proton pump inhibitors omeprazole, lansoprazole and pantoprazole, in humans. *Eur J Drug Metab Pharmacokin* 1998;23:19-26.
- Galmiche JP, Zerbib F, Ducrotte P, Fournet J, Rampal P, Avasthy N, Humphries TJ: Decreasing oesophageal acid exposure in patients with GERD: A comparison of rabeprazole and omeprazole. *Aliment Pharmacol Ther* 2001;15:1343-1350.
- Andersson T, Röhss K, Bredberg E, Hassan-Alin M: Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. *Aliment Pharmacol Ther* 2001;15:1563-1569.
- Ohning GV, Barbuti RC, Kovacs TOG, Sytnik B, Humphries TJ, Walsh JH: Rabeprazole produces rapid, potent, and long-acting inhibition of gastric acid secretion in subjects with *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000;14:701-708.

- 42 Lind T, Rydberg L, Kylebäck A, Jonsson A, Andersson T, Hasselgren G, et al: Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2000;14:861–867.
- 43 McCaffrey E: The acid test for formulary policy. *Bus Health* 1999;17(suppl A):19–24.
- 44 Armstrong D: Long-term safety and efficacy of omeprazole in gastro-oesophageal reflux disease. *Lancet* 2000;356:610–612.
- 45 Holtmann G, Kaspari S, Bayer H, GERD study group: Superiority of pantoprazole (20 mg OD) to omeprazole MUPS (10 mg OD) in patients with mild gastroesophageal reflux disease (abstract). *Gut*, in press.
- 46 Armstrong D: Long-term safety and efficacy of omeprazole in gastro-oesophageal reflux disease. *Lancet* 2000;356:610–612.
- 47 Guyatt GH, Sackett DL, Cook DJ: Users' guides to the medical literature. 2. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1993;270:2598–2601.
- 48 Brouwer WBF, Rutten EFH: GVS geeft verkeerde signalen. *ESB* 2001;86:884–886.
- 49 van Busschbach JJ, van Hout BA: Snel Verdiend: Nieuwe medicatie kan kosteneffectief zijn. *Medisch Contact* 2001;56:1815–1817.
- 50 Vicari F, Belin J, Marek L: Pantoprazole 40 mg versus omeprazole 20 mg in the treatment of reflux esophagitis: Results of a French multicentric double-blind comparative trial (abstract). *Gastroenterology* 1998;114:A324.
- 51 Pilotto A, Franceschi M, Leandro G, Di Mario F, Valerio G: Comparison of omeprazole, lansoprazole, and pantoprazole in the treatment of elderly patients with esophagitis (abstract). *Gastroenterology* 1999;116:A283.
- 52 Hotz J, Gangl A, Heinzerling H: A double-blind study of pantoprazole and omeprazole in the treatment of reflux esophagitis (abstract). *Gastroenterology* 1996;110(suppl):A136.
- 53 Dent J, Brun J, Fendrick AM, Fennerty MB, Janssens J, Kahrlas PJ, Lauritsen K, Reynolds JC, Shaw M, Talley NJ: An evidence-based appraisal of reflux disease management – the Genval Workshop Report. *Gut* 1999;44(suppl 2):S1–S16.
- 54 Scholten T, Gatz G: Pantoprazole 40 mg (Panto) relieves primary reflux symptoms more rapidly than omeprazole MUPS 20 mg (Ome) in patients with severe GERD symptomatology (abstract). *Gastroenterology* 2000;118:A1303.
- 55 Eissele R, Moennikes H, Braun W, Arnold R: Gastrointestinal (GI) symptoms in patients with mild gastro-oesophageal reflux disease (GERD) – effect of pantoprazole (Panto) (abstract). *Gastroenterology* 2000;118:A1231.
- 56 Scholten T, Gatz G, Sander P: Superior symptom relief of pantoprazole 40 mg compared to omeprazole MUPS 20mg in patients with severe heartburn. *Gastroenterol* 2001;120(suppl 1):A440.
- 57 Hungin AP, Rubin G, O'Flanagan H: Factors influencing compliance in long-term proton pump inhibitor therapy in general practice. *Br J Gen Pract* 1999;49:463–464.
- 58 Kroes RM, Numans ME, Jones RH, De Wit NJ, Verheij RJM: Gastro-oesophageal reflux disease in primary care: Comparison and evaluation of existing national guidelines and development of uniform European guidelines. *Eur J Gen Pract* 1999;5:88–97.
- 59 Furuta T, Ohashi K, Kamata T, Takashima M, Kosuge K, Kawasaki T, Hanai H, Kubota T, Ishizaki T, Kaneko E: Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med* 1998;129:1027–1030.
- 60 Howden CW, Burget DW, Hunt RH: A meta-analysis to predict gastric ulcer healing from acid suppression (abstract). *Gastroenterology* 1991;100:A85.
- 61 Lauritsen K, Rutgersson K, Bolling E, Brunner G, Eriksson S, Frison L, Galmiche JP, Thomson ABR, Walan A, Archambault AP, Gudjonsson H, Bailey RJ, Bianchi Porro G: Omeprazole 20 or 40 mg daily for healing of duodenal ulcer? *Eur J Gastroenterol Hepatol* 1992;4:995–1000.
- 62 Beker JA, Bianchi P, Bigard MA, Delle F, Devis G, Gouerou H, Maier C: Double-blind comparison of pantoprazole and omeprazole for the treatment of acute duodenal ulcer. *Eur J Gastroenterol Hepatol* 1995;7:407–410.
- 63 Spencer CM, Faulds D: Esomeprazole. *Drugs* 2000;60:321–329.
- 64 Dobrilla G, Piazzzi L, Fiocca R: Lansoprazole versus omeprazole for duodenal ulcer healing and prevention of relapse: A randomized, multicenter, double-masked trial. *Clin Ther* 1999;21:1321–1332.
- 65 Dekkers CPM, Beker JA, Thjodleifsson B, et al: Comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of active duodenal ulcer: A European multicentre study. *Aliment Pharmacol Ther* 1999;13:179–186.
- 66 Walan A, Bader JP, Classen M, Lamers CB, Piper DW, Rutgersson K, Eriksson S: Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N Engl J Med* 1989;320:69–75.
- 67 Valenzuela JE, Kogut DG, McCullough AJ, Colon P Jr, Shah U, Whipple J, Gilde LR, Simon TJ: Comparison of once-daily doses of omeprazole (40 and 20 mg) and placebo in the treatment of benign gastric ulcer: A multicenter, randomized, double-blind study. *Am J Gastroenterol* 1996;91:2516–2522.
- 68 Witzel L, Gutz H, Huttemann W, Schepp W: Pantoprazole versus omeprazole in the treatment of acute gastric ulcers. *Aliment Pharmacol Ther* 1995;9:19–24.
- 69 Dekkers CP, Beker JA, Thjodleifsson B, et al: Comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of active gastric ulcer – a European multicentre study. The European Rabeprazole Study Group. *Aliment Pharmacol Ther* 1998;12:789–795.
- 70 Bell NJ, Burget D, Howden CW, Wilkinson J, Hunt RH: Appropriate acid suppression for the management of gastro-oesophageal reflux disease. *Digestion* 1992;51(suppl 1):59–67.
- 71 Bate CM, Booth SN, Crowe JP, Hepworth-Jones B, Taylor MD, Richardson PD: Does 40 mg omeprazole daily offer additional benefit over 20 mg daily in patients requiring more than 4 weeks of treatment for symptomatic reflux oesophagitis? *Aliment Pharmacol Ther* 1993;7:501–507.
- 72 Laursen LS, Havelund T, Bondesen S, Hansen J, Sanchez G, Sebelin E, Fenger C, Lauritsen K: Omeprazole in the long-term treatment of gastro-oesophageal reflux disease. A double-blind, randomized dose-finding study. *Scand J Gastroenterol* 1995;30:839–846.
- 73 Hetzel DJ, Dent J, Reed WD, Narielvala FM, Mackinnon M, McCarthy JH, Mitchell B, Beveridge BR, Laurence BH, Gibson GG: Healing and relapse of severe peptic esophagitis after treatment with omeprazole. *Gastroenterology* 1988;95:903–912.
- 74 Astra Pharma Inc. Losec Product Monograph; in: Gillis MC (ed): *Compendium of Pharmaceuticals and Specialties*. Ottawa, Canadian Pharmacists Association, 1998.
- 75 Solvay Pharma Inc/Byk Canada Inc: *Pantoloc Product Monograph*; in Gillis MC (ed): *Compendium of Pharmaceuticals and Specialties*. Ottawa, Canadian Pharmacists Association, 1998.
- 76 Moss SF, Arnold R, Tytgat GNJ, Spechler SJ, Delle Fave G, Rosin D, et al: Consensus statement for management of gastroesophageal reflux disease. *J Clin Gastroenterol* 1998;27:6–12.
- 77 van Rensburg CJ, Honiball PJ, Grundling HD, van Zyl JH, Spies SK, Eloff FP, Simjee AE, Segal I, Botha JF, Cariem AK, Marks IN, Theon I, Bethke TD: Efficacy and tolerability of pantoprazole 40 mg versus 80 mg in patients with reflux oesophagitis. *Aliment Pharmacol Ther* 1996;10:397–401.
- 78 Chiba N: Proton pump inhibitors in acute healing and maintenance of erosive or worse esophagitis: A systematic overview. *Can J Gastroenterol* 1997;11(suppl B):66–73.
- 79 Bardhan KD, van Rensburg C, Gatz G: Comparison of pantoprazole (Panto) 20 mg versus omeprazole (Ome) 20 mg in patients with mild gastroesophageal reflux disease (GERD) (abstract). *Can J Gastroenterol* 1999;13(suppl B):154B.
- 80 Korner T, Suhl DE, Schutze K, Wien AT, van Leendert RJM, Zwijndrecht NL, et al: Comparable efficacy of pantoprazole 40 mg vs. omeprazole MUPS 40 mg in patients with GERD II/III. *Can J Gastroenterol*, in press.
- 81 Bochenek W, Miska D, Beg M: Efficacy of pantoprazole in reflux erosive esophagitis (EE) is dose related (abstract). *Digestion* 1998;59(suppl 3):601.
- 82 Peghini PL, Katz PO, Castell DO: Ranitidine controls nocturnal acid breakthrough on omeprazole: A controlled study in normal subjects. *Gastroenterology* 1998;115:1335–1339.
- 83 Bardhan KD, Van Rensburg C: Comparable clinical efficacy and tolerability of 20 mg pantoprazole and 20 mg omeprazole in patients with grade I reflux oesophagitis. *Aliment Pharmacol Ther* 2001;15:1585–1591.

- 84 Scholten T, Hole U, Gatz G: Similar reduction of symptom load within 4 weeks of treatment with pantoprazole 40 mg or esomeprazole 40 mg in patients with moderate to severe GERD. *Can J Gastroenterol*, in press.
- 85 Eissele R, Gatz G, Hole U: Equivalent efficacy of pantoprazole 40 mg and esomeprazole 40 mg in patients with GERD. *Can J Gastroenterol*, in press.
- 86 Dupas JL, Houcke P, Samoyeau R, et al: Pantoprazole versus lansoprazole in French patients with reflux esophagitis. *Gastroenterol Clin Biol* 2000;25:245–250.
- 87 Sharma VK, Leontiadis GI, Howden CW: Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole. *Aliment Pharmacol Ther* 2001;15:227–231.
- 88 Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, et al: Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: A randomized controlled trial. *Aliment Pharmacol Ther* 2000;14:1249–1258.
- 89 Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, et al: Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: A randomized controlled trial. *Am J Gastroenterol* 2001;96:656–665.
- 90 Kromer W, Horbach S, Luhmann R: Relative efficacies of gastric proton pump inhibitors: Their clinical and pharmacological basis. *Pharmacology* 1999;59:57–77.
- 91 Jones R, Bytzer P: Review article: Acid suppression in the management of gastro-oesophageal disease – an appraisal of treatment options in primary care. *Aliment Pharmacol Ther* 2001;15:765–772.
- 92 Byrne MF, Murray FE: Formulary management of proton pump inhibitors. *Pharmacoeconomics* 1999;16:225–246.
- 93 Panto™ IV product monograph.