**SUMMARY**

Proton pump inhibitors have dramatically improved the management options available for patients with acid-related disorders.

In patients with gastro-oesophageal reflux disease, currently available proton pump inhibitors provide an excellent outcome for the majority; however, they do not provide optimal pH control in many. Proton pump inhibitors co-therapy reduces, but does not eliminate, the risk of gastrointestinal ulcers and complications in patients taking non-steroidal anti-inflammatory drugs, while in patients with upper gastrointestinal bleeding, it may be difficult to reach and maintain the current therapeutic target of intragastric pH of 6–7.

This article reviews the effectiveness of current antisecretory therapy in these three acid-related diseases and areas of unmet clinical need. The potential role of a proton pump inhibitor with an extended duration of action and enhanced acid control from a single daily dose, particularly improved control at night, is discussed. Finally, therapy that could be administered without regard to time of day and/or food intake would offer dosing flexibility and thus have a positive effect on patients’ compliance.
INTRODUCTION

Proton pump inhibitors (PPIs) have dramatically improved the management options available for patients with acid-related disorders. In the management of gastro-oesophageal reflux disease (GERD), PPIs offer the opportunity of effective symptom control and healing of oesophagitis in the majority of patients. Clinical studies have also demonstrated the effectiveness of PPIs in providing acid suppression as part of a regimen which includes antibiotics for Helicobacter pylori (H. pylori) eradication, and as a gastroprotective therapy for patients taking non-steroidal anti-inflammatory drugs (NSAIDs), and both i.v. and oral PPIs are utilized in the management of upper gastrointestinal (GI), non-variceal bleeding. This review will consider whether the currently available PPIs meet therapeutic expectations in three of these settings, and the unmet areas of clinical need that remain.

PHARMACOLOGICAL PROFILE OF PPIs

Optimal understanding of the efficacy of the PPIs requires a short review of their pharmacology. PPIs are weak protonatable bases, incompletely absorbed because of acid breakdown during their passage through the stomach. In general, they have half-lives of <90 min and are accumulated and activated in the acidic milieu on the secretory canalicular surface of the parietal cell. The drugs covalently bind to cysteine residues on the alpha subunit of the H⁺K⁺ATPase enzyme, thus irreversibly inhibiting acid production. The ability of the parietal cell to secrete acid is restored when new proton pumps are converted from their inactive status in the tubulovesicle to their active form resulting in their location to the canalicular surface. Not all pumps are active at any given time, and it is thought that a single dose of a PPI will inhibit only 70–80% of active pumps. Thus, PPIs do not completely inhibit acid secretion. Because proton pumps are always in the process of regeneration, daily or more frequent dosing may be needed to achieve optimal antisecretory effect. Full restoration of antisecretory effect takes about 96 h in healthy subjects. In general, the actively secreting ATPase molecules are inhibited such that the timing of the dose in relationship to a meal is believed to be critical. In addition, the efficacy of intragastric pH control may be dependent on H. pylori status, and/or genetic variation in the hepatic cytochrome P450 enzyme system, specifically polymorphism in the CYP3A4 and CYP2C19 enzymes. There may also be differences in intragastric pH control in different ethnic groups. While the clinical implications of these differences in large populations are unknown and remain to be explored, the pharmacological actions of these drugs are crucial to understanding how they might be improved.

Numerous studies have evaluated the pharmacodynamic profiles of the currently available PPIs. There is a substantial inter-individual variability in intragastric pH control from study to study, making it important that cross-over studies, in which patients are their own controls, are used to make adequate comparisons between drugs and to understand their overall efficacy. The general conclusion from these individual studies is that intragastric pH control is most effective when delayed-release PPIs are given prior to a meal. One study in which 20 subjects were randomized to omeprazole 20 mg or lansoprazole 30 mg in the morning either 15 min before a breakfast meal or without food or drink except for water until 12:00 noon showed statistical improvement in intragastric pH control when the dose was given before a breakfast meal rather than in the morning with no food until lunch (Figure 1). The new immediate-release formulation or omeprazole (IR-OME) offers the opportunity to eliminate the need for meal timing, but it remains to be seen whether dosing with this formulation before bedtime will result in improved outcomes or even 24-h pH control when a proton pump inhibitor (PPI) is taken prior to breakfast rather than without a morning meal. The box (25–75%) indicates the wide variation in pH control between individual subjects.
control. So, there is still a need for an agent with maximal efficacy irrespective of time of day and/or food intake.

In general, control of intragastric acid is best during the waking hours when meals are ingested with an overall loss of pH control during the overnight period. A retrospective review of the intragastric pH profiles in healthy subjects given single daily doses of omeprazole, lansoprazole, rabeprazole or pantoprazole produced the intragastric pH profiles illustrated in Figure 2.4 The newest PPIs, esomeprazole and IR-OME, exhibit similar pH profiles, albeit with some differences in overall pH control.

An often-quoted study is the five-arm, randomized, cross-over study in which 34 H. pylori-negative patients with GERD were given, in random order, esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and omeprazole 20 mg once-daily before breakfast for 5 days, with a washout period of 10–17 days between treatments.5 The key results of this trial, illustrated in Figure 3, indicated that control of intragastric pH with esomeprazole 40 mg/day is slightly superior to the other PPIs. However, notably, in this H. pylori-negative cohort, there was still a substantial portion of the day in which the intragastric pH fell below 4.

UNMET NEEDS IN GERD

The treatment of GERD has advanced considerably over the past two decades. Our current antisecretory therapy, principally with PPIs, either alone or in combination with H2RAs, has allowed us to reach a point where the vast majority of patients can be effectively managed.

However, these therapies have shortcomings. There is still a subset of patients in whom erosive oesophagitis remains unhealed after 8 weeks of therapy with once-daily PPIs. This is particularly true in those with grade C and D erosive disease (Figure 4).6–10 A substantial percentage of patients on once-daily PPIs self-report incomplete symptom control despite therapy with these excellent drugs (Figure 5). Furthermore, long-term maintenance studies show consistently that 10–20% of patients on the best once-daily PPI will relapse within 6 months.11–13 An increasing number of patients with Barrett’s oesophagus are being identified and current medical therapy offers little to alter the natural history of this disease. There is a heightened awareness of the frequency of nocturnal reflux and nocturnal heartburn and their attendant potential complications such as severe erosive oesophagitis, nocturnal aspiration and a greater likelihood of Barrett’s oesophagus. The awareness of sleep disorders and their association with GERD,4 and the overall decrease in quality-of-life seen with nocturnal reflux,14 have highlighted the need to improve the management of these patients. In the five-arm cross-over study described above, intragastric pH fell below 4 for a mean of 10–14 h in 24, most commonly during the sleeping period.5 This suggests a possible explanation as to why some patients will not
heal their oesophagitis or experience symptom relief on once-daily PPI therapy; acid control may be insufficient to achieve these goals. There are also have groups of patients who present with symptoms other than heartburn and regurgitation, i.e. those with so-called extra-oesophageal disease, including non-cardiac chest pain, chronic laryngitis and other ENT manifestations of GERD such as cough and asthma, for whom we have been unable to maximally relieve symptoms.

Strategies to optimize pH control with existing PPIs

It could be argued that these unmet therapeutic needs in GERD therapy are underscored by some of the shortcomings or ‘soft spots’ of current antisecretory therapy and the ability to control intragastric pH. IR-OME powder for oral suspension, a formulation of non-enterically coated omeprazole protected from acid degradation by sodium bicarbonate, has offered intriguing possibilities for control of nocturnal acidity. The postulate that rapid alkalinization of gastric contents by the sodium bicarbonate as a means of activating proton pumps more quickly which in turn are inhibited by the peak plasma concentrations of omeprazole is the backbone of the theory behind the potential effectiveness of this new formulation. A recent randomized, open-label, cross-over trial, comparing IR-OME and delayed-release pantoprazole in 36 patients with night-time GERD symptoms, reported enhanced control of night-time intragastric pH with the immediate-release compound compared with pantoprazole at steady state.15 IR-OME 40 mg and pantoprazole 40 mg were given once-daily (at bedtime or before dinner, respectively) for 6 days, followed by twice-daily dosing (before breakfast and at bedtime) on day 7. At the end of 6 days, the median percent time intragastric pH was >4 between 10:00 PM and 6:00 AM was superior for IR–OME compared with pantoprazole (55% vs. 27%, P < 0.001). Despite this improved overnight pH control with the bedtime-dosing regimen, daytime pH control with IR-OME was equivalent to that expected with the delayed-release omeprazole. While IR-OME was clearly superior to pantoprazole in this study, many patients still demonstrated overnight acid recovery. Thus, there is still a need for a once-daily PPI that will provide better night-time acid control.
Increasing the dose of a PPI will increase intragastric pH control; however, even twice-daily dosing of PPIs will fail to adequately control intragastric pH in many patients. A cross-over study compared esomeprazole (20, 40 and 80 mg) given once-daily before breakfast with lansoprazole (15, 30 and 60 mg) in the control of intragastric pH over 24 h. The 80-mg once-daily esomeprazole dose achieved intragastric pH control for only 16 h out of 24, which, while superior to lansoprazole 60 mg, is substantially less than can be achieved with twice-daily dosing. The few studies that have looked at the effect of these so-called double doses given once-daily in healing of erosive oesophagitis have shown only a small incremental benefit over the usual once-daily doses of the currently available PPIs.

Intragastric pH monitoring studies have clearly shown that splitting the PPI dose, giving a dose before breakfast and a second dose before the dinner meal, is the most efficacious way to optimize intragastric pH control compared with once-daily morning dosing. This is illustrated by a study that randomized 18 healthy subjects to receive omeprazole 40 mg before breakfast, 40 mg before dinner, or 20 mg before breakfast and before dinner for 7 days. In this cross-over study, daytime intragastric pH control was similar with all three regimens; however, intragastric pH control in the overnight period was significantly improved with twice-daily dosing compared with the single dose at either time (Figure 6). Nonetheless, even on twice-daily PPI, a substantial number of subjects had a dramatic drop in pH to <4 during the sleeping period. In fact, over 70% of these subjects had more than one continuous hour with intragastric pH below 4 while they were asleep. This so-called nocturnal gastric acid breakthrough (NAB) was associated with oesophageal reflux in only a minority of these normal subjects. While the clinical importance of NAB is much debated, studies have shown that 15% of patients with GERD will have some oesophageal reflux during NAB, 50% of patients with Barrett’s oesophagus will have overnight oesophageal reflux despite even twice-daily PPI, and close to 70% of patients with scleroderma will have oesophageal reflux in the overnight period during periods of NAB.

In patients with Barrett’s oesophagus, the clinical implications of the lack of overnight pH control on twice-daily PPIs may be significant. Studies using markers of cellular proliferation have demonstrated a decrease in cell turnover in patients with effective control of oesophageal acid exposure, and a recent study has revealed a decrease in the rate of development of dysplasia in patients treated with PPIs compared with those treated with H₂RAs or no regular antisecretory therapy. These studies have led many to conjecture that aggressive control of oesophageal acid exposure in patients with Barrett’s oesophagus might positively affect the natural history of the disease and perhaps decrease the development of dysplasia and oesophageal carcinoma. Unfortunately, recent studies have shown that oesophageal acid exposure can be normalized in only 80–85% of patients with Barrett’s oesophagus treated with twice-daily PPIs (Figure 7). In this setting, and in patients with other forms of refractory GERD, overnight breakthrough of gastric acid is clearly of clinical importance.

Attempts to eliminate NAB have included the use of H₂RAs at bedtime in conjunction with PPIs and/or using IR-OME at bedtime. In the aforementioned trial of IR-OME, after 7-day therapy the median time intragastric pH was >4 was superior to IR-OME compared with pantoprazole (92% vs. 37%, respectively; P < 0.001). In addition, the median night-time gastric pH was higher with IR-OME than with pantoprazole (5 vs. 2; P < 0.001). It must be noted, however, that overnight pH control was not universal – a substantial proportion of the cohort still experienced NAB – and there have been no outcomes studies to indicate whether this strategy will provide sufficient control of intragastric or intra-oesophageal acid.

![Figure 6. Twice-daily omeprazole resulted in better overnight pH control compared with once-daily dosing before breakfast or dinner.](image-url)
H₂RAs are extremely effective in eliminating NAB in the short term. In fact, a single dose of ranitidine 150 or 300 mg given at the hour of sleep will essentially eliminate NAB in almost all patients. Unfortunately, regular use of H₂RAs at bedtime may result in tachyphylaxis in a substantial proportion of patients. In clinical experience, approximately 25–30% of patients will achieve sustained intragastric pH control when H₂RAs are used at bedtime in conjunction with twice-daily PPIs, while the remainder, the majority, will have some loss of benefit. Thus, while effective in controlling intermittent night-time heartburn in some, even many, this intervention does not offer consistent long-term control for every patient.

In the multiple pharmacodynamic studies in the literature, there is an undiscussed but large inter-individual and intra-individual variability in intragastric pH control with the available PPIs whether given once- or twice-daily. For example, Figure 8 shows wide variability in 24-h pH control achieved with either omeprazole 20 mg b.d. or lansoprazole 30 mg b.d., as well as intra-subject variability, with some patients responding well to omeprazole but not lansoprazole, and the reverse. In practice, this inter-individual variability is similar with all the available PPIs. While this inter- and intra-subject variability may not be of major clinical importance when evaluating large groups of patients, as in erosive oesophagitis healing trials, the variability of response to PPIs clearly has clinical implications in the individual patient.

UNMET NEEDS IN THE PREVENTION AND MANAGEMENT OF NSAID-ASSOCIATED GASTROPATHY

While NSAIDs provide relief of pain and inflammation, they increase the risk of GI side effects ranging from dyspepsia to complicated ulcers. Although the absolute risk of serious GI complications from NSAID therapy is relatively low, their widespread use makes NSAID-associated GI adverse effects the most common serious drug-related toxicity. The coxibs [selective COX-2 (cyclooxygenase-2)] inhibitors [COX-2] were developed to provide pain relief equivalent to that achieved by traditional NSAIDs, but with a reduced rate of adverse GI outcomes. With the recent withdrawal of rofecoxib and valdecoxib from the market, a review of strategies to reduce the overall risks of therapy in patients taking anti-inflammatory drugs is timely.

The incidence of endoscopic ulcers in NSAID takers ranges from 15% to 25%, and although 1–4% develop a symptomatic ulcer, the risk varies considerably across patient profiles. Symptoms, or the lack thereof, are not good predictors of NSAID complication risk. In clinical practice, it is therefore essential to assess the individual’s risk for complications (Table 1). At present, however, there is no ‘optimal’ management approach that simultaneously yields high
levels of analgesia and anti-inflammatory activity with no undesirable outcomes.

**COX-2 selective inhibitors (coxibs)**

The coxibs added an important new option to reduce the clinical and economic burden of NSAID-induced gastropathy. These agents have similar efficacy to traditional NSAIDs and an improved GI safety profile (in the absence of low-dose aspirin). Their availability changed the paradigm of management of patients requiring NSAIDs, particularly those with an increased risk for NSAID-related events. This improvement in GI outcomes was validated with the findings of large outcomes trials, CLASS (Celecoxib Long-Term Arthritis Safety Study), VIGOR (Vioxx Gastrointestinal Outcomes Research Study), and TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial), which all found statistically significantly lower rates of symptomatic GI events for the coxib evaluated compared with traditional NSAID therapy. However, secondary analyses of these trials confirmed that among patients with advancing age, or multiple risk factors, serious events continued to occur at unacceptably high rates (Figure 9).

**Co-therapy with a GI protective agent to prevent NSAID-related ulcers**

Prostaglandin depletion is a central mechanism for the development of NSAID-related ulcers, and replacement therapy with the synthetic prostaglandin, misoprostol, reduces NSAID toxicity. Although it is the only FDA-approved regimen for prevention of both NSAID ulcers and complications, it is rarely used because of side effects of diarrhea and abdominal cramping.

An alternative strategy is to protect the GI mucosa from damage through acid suppression. It is known that maintaining intragastric pH above 4 heals gastric ulcers, and also that in patients receiving NSAIDs the extent of NSAID-associated gastric damage is pH dependent. The level of acid suppression provided by traditional doses of H2RAs does not prevent most NSAID-related gastric ulcers. Despite a single study demonstrating that H2RAs at double the usual dose may be effective, there are no published studies comparing high doses of H2 blockers to misoprostol or PPIs for the prevention of NSAID-associated ulcers. However, once-daily PPI therapy has been proven superior to both twice-daily H2RA therapy and misoprostol for healing NSAID-associated gastric and duodenal ulcers. Maintenance trials in patients continuing to take NSAIDs have also demonstrated the superiority of PPI therapy over ranitidine or misoprostol in preventing NSAID-associated ulcer recurrence and overall symptom control, largely related to the ability of PPIs to reduce ulcers and improve NSAID-associated

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**Table 1. Risk factors for aspirin– and non-steroidal anti-inflammatory drugs (NSAID)-associated ulcer complications (in order of relative importance)**

1. Personal history of complicated ulcer disease
2. Concurrent use of >1 NSAID (including aspirin)
3. Use of high doses of NSAID(s)
4. Concurrent use of an anticoagulant
5. Personal history of uncomplicated peptic ulcer disease
6. Age >70 years
7. Concurrent use of steroids

**Figure 9.** The effect of (a) age and (b) risk factors on clinical events in coxib outcome trials.
dyspepsia thereby improving overall quality-of-life.48–51 However, in these studies of between 12- and 24-week duration, patients in all arms suffered relapses. After 12 weeks, approximately 20% of 

\( H. pylori \) negative patients healed with a PPI suffered an ulcer relapse despite receiving lansoprazole,50 while ulcer rates at 24 weeks in patients receiving omeprazole maintenance therapy were 13% for gastric ulcer and 3% for duodenal ulcer.47 Most NSAIDs are dosed twice-daily or formulated to provide 24-h analgesia, yet, even at steady state, current PPIs dosed once-daily hold the gastric pH below 4 for only 60–70% of a 24-h period. This suggests that for a substantial proportion of the day (or night), patients are not protected from their NSAID-related adverse GI effects.

Chan et al. randomized 287 of the NSAID takers with the highest risk – those with a history of ulcer bleeding – to either a PPI (omeprazole 20 mg) with a traditional NSAID (diclofenac 75 mg b.d.) or celecoxib 200 mg bid for 6 months.52 All patients were 

\( H. pylori \)-negative. No significant difference was found in the number of patients re-presenting with an ulcer bleed: 5% of the coxib group (95% CI: 3–7) and 6% of those taking diclofenac with a PPI (95% CI: 4–8). While this study was not powered to demonstrate equivalence, the results suggest that the strategies were similar in efficacy and neither regimen was sufficient to protect this high-risk group of patients. Indeed, a follow-up endoscopy performed at 6 months in those without a recurrent complication revealed ulcer rates of 19% and 26% in the celecoxib and diclofenac plus PPI-treated patients, respectively. On the basis of such data, experts recommend these patients at highest risk receive co-therapy with a PPI (or misoprostol) in addition to a coxib to provide multiple risk-reducing strategies.

Recently completed studies of 

\( H. pylori \)-negative patients at increased risk of developing ulcers (age >60 years or recent gastric or duodenal ulcer) have shown PPI co-therapy can be effective in preventing ulcer development in patients taking coxibs or non-selective NSAIDs.53 Among the cohort taking coxibs, very few ulcers were seen in those who also received esomeprazole, while those taking a coxib plus placebo experienced similar rates of ulcer recurrence to those taking traditional NSAIDs plus the PPI (Figure 10). These results emphasize that patients at increased risk of GI complications who are taking coxibs still have considerable residual ulcer risk, and point to the value of using the safer NSAID (i.e. coxib) with PPI co-therapy.

Recently, a multidisciplinary group met to discuss contemporary strategies for NSAID use.54 The avoidance of COX-2-selective NSAIDs is recommended for patients with cardiovascular risk. The use of COX-2 inhibitors and/or gastroprotective therapy is, however, recommended for patients who are at risk of GI injury. Furthermore, a careful risk–benefit assessment is recommended prior to the use of aspirin. Despite these approaches, current PPI therapy does not protect all patients from GI complications and new agents providing prolonged or improved acid suppression may more effectively protect patients from ulcers and complications.

UNMET CLINICAL NEEDS IN THE MANAGEMENT OF UPPER GI BLEEDING

Upper GI bleeding occurs in North America with a prevalence of approximately 100 cases per 100 000 adults per year. The advent of newer endoscopic therapies and more profound acid suppression have provided further possibilities for improving outcomes in patients with upper GI bleeding, most of which are attributable to erosions or ulcers.55,56

It has been shown that acid impairs clot formation as it inhibits platelet aggregation and even causes platelet disaggregation.57 A pH of at least 6 is required to achieve a significant reversal of this effect based on \textit{in vitro} and animal studies.58 Acid also accelerates clot lysis through a predominantly acid-stimulated pepsin mechanism,59 while it has also been shown that acid
suppression may favour antifibrinolysis. It has thus been postulated that acid suppression may stabilize intraluminal clot with a subsequent improvement in outcomes in patients with upper GI bleeding. A number of gastric pH studies, performed for the most part in normal volunteers, demonstrated the superior clinical effectiveness of continuous i.v. PPI infusion in achieving a sustained target gastric pH of 6, with a resulting optimal dose of 80 mg bolus followed by 8 mg/h using either omeprazole or pantoprazole. More recent data have, however, suggested more modest clinical efficacy of i.v. PPI preparations in a contemporary North American population. The clinical implications of these results, especially in the face of limited randomized controlled trial (RCT) data from North America, will require further study. Fully published comparative gastric pH studies between high-dose oral and i.v. PPI preparations are also lacking, especially in high doses and in patients with peptic ulcer bleeding.

The role of H2RAs and PPI in peptic ulcer bleeding

A large randomized clinical trial and two meta-analyses have shown minimal or no benefit attributable to the acute use of H2RAs in patients with peptic ulcer bleeding. Statistically significant but very modest benefits in re-bleeding and decreased surgical rates were found in a subgroup of patients with bleeding gastric ulcers, but no significant lowering of mortality was noted. The main reasons for this lack of efficacy include the modest acid suppression attributable to H2RAs, and perhaps most importantly, the rapid development of pharmacological tolerance to these medications that occur as early as 24 h after the onset of therapy. This is especially pertinent as clot stabilization by acid suppression is required for up to 72 h to decrease re-bleeding in patients with high-risk ulcers undergoing endoscopic haemostasis. It is because of these data that the use of H2RA in the routine management of patients with acute peptic ulcer bleeding is not recommended. Intravenous PPIs achieve more profound and sustained acid suppression than H2RAs without the development of tolerance. Well-designed randomized controlled trials have shown the efficacy of high-dose PPI infusions (80-mg bolus followed by 8 mg/h for the first 3 days of treatment) following endoscopic therapy for patients with bleeding ulcers and high-risk stigmata. showed a decrease in the re-bleeding rate from 22% in the placebo group to 7% in the high-dose i.v. omeprazole group (hazard ratio = 4, 95% CI: 2–9) with trends in improvements for surgery and even mortality.

More recently, a number of systematic reviews have summarized the clinical experience with PPI in patients with peptic ulcer bleeding. An authoritative Cochrane meta-analysis included 21 randomized controlled trials comprising 2915 patients. PPI did not affect mortality despite reducing rebleeding (0.46, 0.33–0.64; NNT 12) and surgery (1, 0.46–0.76; NNT 20). Additional meta-analyses found similar results and suggested no dose-related difference in efficacy, although this interpretation may, in fact, be flawed. When one outlying study is removed from analysis, it appears that high-dose PPI may improve mortality, a finding that has been suggested by real-life effectiveness results in a large national registry. Summary attributable improvements in transfusion requirements and duration in hospital stay have also been reported. The assumptions and controversies brought out by meta-analytical and effectiveness study results emphasize the unknown nature of any possible optimal dose threshold. At this time, it would appear that high-dose PPI therapy needs to be considered an adjuvant to endoscopic haemostasis. However, a recently completed study suggested that sole PPI therapy may be sufficient in a subgroup of patients found to be bleeding from peptic ulcers exhibiting adherent clots. The study, however, was not designed to definitively answer this specific question, which remains controversial in the light of discrepant views on the risk of rebleeding of this endoscopic lesion and the results of two RCTs confirming the efficacy of combined endoscopic therapy in this setting. The role of high-dose oral PPI in the acute management of patients with bleeding ulcers remains more controversial and the efficacy of these may vary depending on H. pylori prevalence in the target patient population as well as physiological and pharmacokinetic differences. Indeed, data from Asia suggest efficacy of high-dose oral omeprazole (a daily total of 80 mg) while high-quality corresponding studies from Caucasian populations are still few.

Based on all available data, authoritative consensus guidelines have endorsed the use of high-dose i.v. PPI in the routine management of patients undergoing endoscopic haemostasis for a high-risk peptic ulcer bleeding lesion. Decision models and cost studies
have confirmed the cost-effectiveness of using i.v. high-dose PPI following endoscopic haemostasis for patients with bleeding ulcers that exhibit high-risk stigmata in most adopted clinical scenarios. Whether the routine administration of i.v. PPI prior to endoscopy is cost-effectiveness or not is controversial and awaits fully published results of a recently completed clinical study. Current additional important issues pertain to the appropriate use of PPI in the hospital setting, indeed, the inappropriate use of these agents is quite high (30–70%), potentially negating their proven cost-effectiveness, especially when considering potential side effects, even if the risk–benefit ratio of these medications remains extremely favourable.

CONCLUSION

Currently available PPIs have improved outcomes in a number of acid-related disorders, including those described here. However, while currently available antisecretory therapy provides an excellent outcome for the majority of patients with GERD, there are clearly areas in which improvement in our ability to control intragastric pH might bring positive benefit in the clinical arena. Improved overnight pH control with once-daily PPIs might afford improvement in healing of erosive oesophagitis, particularly the higher grades, overall improvement in complete symptom relief, and improvement in residual nocturnal heartburn. This might reduce the decrease in quality-of-life seen in patients with nocturnal GERD symptoms and, perhaps, improve the sleep abnormalities seen in this population. While control of intragastric pH and subsequent oesophageal acid exposure can be substantially improved with twice-daily PPI dosing, adding an H2 blocker at bedtime or combinations including IR-OME, there remain a substantial number of refractory patients and patients with Barrett’s oesophagus who may clearly benefit from better antisecretory control, or in whom a truly once-daily therapy could offer symptom relief without the need for twice-daily or multiple medications.

For patients receiving NSAIDs, PPI co-therapy reduces, but does not eliminate the risk of GI ulcers and complications. By maintaining the gastric pH above 4 for a longer duration, improved acid suppression may provide additional mucosal protection and maintain ulcer healing in patients continuing to require analgesia. However, in patients with very high levels of risk, additional protective measures, including the use of coxibs, should be considered.

In the management of patients with upper GI bleeding, recent data suggest that, at least in North American patients, it may be difficult to reach and maintain the current therapeutic target of intragastric pH of 6–7, although data in patients with bleeding peptic ulcers are lacking. Furthermore, the optimal timing of acute PPI dose (pre- and postendoscopy), dose regimen (early bolus, continuous infusion, duration of 72 h or less) and the route of administration all require better characterization. For patients with adherent clots a sole PPI therapy (i.e. without associated endoscopic therapy) could be optimal, however, it is unlikely that this would be sufficient in bleeding ulcer patients with higher risk endoscopic lesions. Finally, an orally administered PPI with a comparable or better overall efficacy than the existing i.v. preparations may have the potential for improved outcomes.

An antisecretory therapy that could be administered without regard to time of day and/or food intake would offer dosing flexibility that would clearly have a positive effect on patients’ compliance. This would be especially valuable for patients using intermittent or on-demand therapy, particularly those who experience exacerbations of symptoms at times of stress or dietary indiscretion.

The marked inter-individual variability in pH response may have important implications for the patient who ‘fails to respond’ to a particular PPI. The need to switch PPIs or increase the dose might be eliminated if this inter-individual variability could be decreased. We look forward to the development of new therapies that satisfy these unmet needs.

FINANCIAL DISCLOSURE

Philip Katz is a consultant for Novartis, Eisai and Negma-Lerads. He has also been a speaker and received honoraria for lectures from AstraZeneca, Santarus and TAP, and research funds from AstraZeneca. James Scheiman has received research support and acts as a consultant to AstraZeneca. He has also acted as a consultant to Bayer, GSK, McNeil, Merck, Novartis, Pfizer, Pozen, TAP and The GI Company. He has also been a speaker and received honoraria from AstraZeneca, Santarus and TAP. Alan Barkun has acted as a consultant for Altana Pharma Canada, and for AstraZeneca Canada. He has also received research support (grants) from AstraZeneca.
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