REVIEW ARTICLE

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Intravenous Proton Pump Inhibitors

An Evidence-Based Review of Their Use in Gastrointestinal Disorders

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Abstract

Conditions requiring inhibition of acid secretion, such as gastro-oesophageal reflux disease or peptic ulcers, are very common and their prevalence is expected to rise as they are seen predominantly in the elderly.

The general basis of treatment with antisecretory agents is to maintain gastric pH >4 for a substantial proportion of the 24-hour cycle. Among the drugs available to inhibit acid secretion, proton pump inhibitors (PPIs) have been shown to have the best benefit-risk ratio and have been used widely. Intravenous administration of a PPI provides gastric acid suppression faster than oral administration does. Whereas some indications for the use of

intravenous PPIs are widely known, mostly for acute management of peptic ulcer bleeding, there are some controversies surrounding their use in other conditions such as stress-induced mucosal damage.

There is still a need to define the best schedule for intravenous PPI administration (i.e. bolus infusion or constant infusion), the optimal time to switch from intravenous to oral administration and the choice of which agent is best. In most of the clinical scenarios where PPIs are recommended, they can be administered via either oral or enteral routes, unless the patient is nil by mouth.

Since there are no head-to-head comparisons of the different intravenous PPIs available worldwide (omeprazole, lansoprazole, pantoprazole and esomeprazole), the rule might be to choose the drug with the best proven efficacy in each specific condition. Indeed, the key difference between them, the ability to reach and to maintain a threshold gastric pH, might not necessarily translate into clinically significant differences.

Conditions requiring inhibition of acid secretion that may warrant the use of proton pump inhibitors (PPIs), such as gastro-oesophageal reflux disease (GORD) and peptic ulcer diseases, including prevention of NSAID-induced ulcers or treatment of upper gastrointestinal haemorrhage (UGIH) and the eradication of *Helicobacter pylori*, are very common and their prevalence is expected to rise because most of them are seen predominantly in the elderly. Some other purported uses for PPIs are more controversial, such as non-ulcer (or functional) dyspepsia, and prevention of stress-induced mucosal damage in critical care or surgical patients.

The general basis of treatment with antisecretory agents is to maintain gastric pH >4 for a substantial proportion of the 24-hour cycle. Among the drugs available to inhibit acid secretion, PPIs have been shown to have the best benefit-risk ratio and have been used widely.

For the majority of patients who require PPIs, oral therapy is effective; nevertheless, some patients cannot take oral PPIs (for example, those with frequent emesis, nil by mouth or critical illness) and intravenous PPIs may be required.

Many hospitalized patients receive acid suppressive agents and a hospital audit conducted in the USA in 1998 showed that over 4.2 million critical care patients received intravenous acid-suppressive therapy during this year. Stress ulcer prophylaxis was the most common condition (44%) in critical care patients receiving acid suppression. Other conditions in which intravenous acid suppression was used included presurgical aspiration-pneumonia prophylaxis (21%), UGIH (12%), duodenal ulcer, gastric ulcer, GORD or gastritis (10%), and acute pancreatitis (8%).[1]

For patients with nonvariceal UGIH, profound acid suppression (gastric pH >6.0) optimizes clot stability and reduces the risk of rebleeding; this is achieved most effectively with an initial intravenous PPI bolus followed by a continuous infusion.[2,3] High-dose, intravenous PPI therapy is beneficial[4] and cost effective[5] in patients who have a high-risk lesion at endoscopy and it should be preceded by effective endoscopic haemostasis if possible.[6] Intravenous PPIs, preoperatively and in the intensive care setting, effectively reduce gastric acidity; however, studies to date have not proven that this confers any significant clinical benefit compared with other therapeutic strategies.[7-9]

1. Pharmacology of Proton Pump Inhibitors (PPIs)

1.1 Pharmacodynamics

Proton pumps belong to the super family of ion transporters using the adenosine triphosphate (ATP) phosphorylation-dephosphorylation reaction and are located on the cytoplasmic membrane of gastric parietal cell canaliculi. At steady state, non-activated proton pumps are

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located within the cytoplasm and, when activated, migrate to the lumen to exchange one H^+ ion for a K^+ ion. Chloride is secreted at the same time to form a hydrogen chloride molecule.

PPIs are of particular therapeutic importance since they inhibit the activity of the gastric acid pump (H^+,K^+-ATP), the final common step in gastric acid production. PPIs are substituted benzimidazole derivatives and weak bases, which undergo accumulation in the acidic space of the secreting parietal cell before being converted in the canuliculi of the gastric parietal cell, an acidic environment, to active sulfenamide derivatives. This active thiophilic form then forms disulfide bonds with key cysteins of the gastric acid pump.

There are five PPIs commercially available: omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole. All, except rabeprazole, are available in oral and intravenous formulations. Because PPIs bind covalently to the proton pump, restoration of acid secretion after treatment with PPIs depends on protein turnover and on reversal of inhibition by reducing agents such as glutathione.[10] As a result, despite a short plasma half-live of about 1–2 hours, PPIs can be used on a once-daily basis. The pharmacodynamic effect of PPI on gastric acid secretion increases during the initial days of treatment and reaches a plateau by the third to fifth day of treatment.

Therapeutic efficacy for gastric acid suppressants for acid-related pathology is generally correlated with the degree and duration of acid suppression over 24 hours,[11,12] and recommended dosages of PPIs (i.e. 20 mg daily for omeprazole, 30 mg daily for lansoprazole or rabeprazole, and 40 mg once daily for pantoprazole or esomeprazole) maintain gastric pH >4 for 10–14 hours.

1.2 Pharmacokinetics

Pharmacokinetic studies comparing the oral and intravenous administration of PPIs have shown that intravenous administration was associated with a 2-fold higher peak concentration and a 66–83% greater area under the plasma concentration-time curve compared with oral administration of the same single dose. As a result of the increased bioavailability of oral PPIs after repeated use, differences were similar but slightly less pronounced after repeated daily administration for 5 days.[13] Nonetheless, these differences in kinetics did not translate into differences in pH control since no significant differences were found between intravenous or oral administration of esomeprazole with respect to the amount of time with mean intragastric pH >4 throughout day 1 or day 5 of treatment.[14]

PPIs are about 97% bound to protein and the apparent volume of distribution at steady state is approximately 16 L.[15] Omeprazole, lansoprazole, pantoprazole and esomeprazole are metabolized in the liver through the cytochrome P450 (CYP) 2C19 enzyme system. In individuals with genetic CYP2C19 deficiency (i.e. 3% of Caucasian and Africans, and 17–23% of Asians), the elimination half-life is increased by 2- to 4-fold.[15]

2. Translating Pharmacokinetics into Clinical Practice: Some Concerns Surrounding the Use of Intravenous PPIs

2.1 Intermittent Injection or Continuous Infusion?

It is not easy to comment on the relative efficacy of intravenous bolus versus constant infusion since there are few studies where the same dose was administered via the two different modalities. For example, a subanalysis was conducted of patients with bleeding peptic ulcers who underwent continuous monitoring of gastric pH while receiving intravenous omeprazole either by intermittent injection or continuous infusion (20 mg intravenous bolus three times a day vs 80 mg bolus + 8 mg/hour infusion, regular and high-dose, respectively). The analysis showed that the regular dose of omeprazole was able to increase the mean and median 24-hour intragastric pH >4 to an extent that is probably sufficient to maintain haemostasis in patients with bleeding peptic ulcers,[16] even if high-dose omeprazole maintained the pH almost constantly >6,

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which has been suggested to provide greater physiological protection to the gastric mucosa during acute UGIH. Another clinical study conducted in 153 patients with bleeding peptic ulcers compared pantoprazole constant infusion (80 mg bolus + 8 mg/h infusion for 3 days) with pantoprazole bolus administration (80 mg intravenous bolus followed by 40 mg intravenous bolus every 12 hours for 3 days) or no treatment.[17] This study showed that both regimens of pantoprazole were superior to no treatment for pH control and rebleeding rates, and were not different from each other.

Data suggesting that an injection (3 minutes) or an infusion (30 minutes) result in similar efficacy have been demonstrated in pH studies conducted in healthy volunteers, showing that intravenous esomeprazole 40 mg provides similarly potent acid control whether administered by injection or infusion,[14] and from a clinical study conducted in patients with erosive oesophagitis, suggesting that healing rates were similar after 4 weeks.[18]

Thus, it could be suggested that a high-dose constant infusion may be more beneficial (based on pH and physiology, and not yet definitively proven by head-to-head trials) than intravenous bolus therapy, and if it is, only in peptic ulcer bleeding where the target pH value is >6. Otherwise, when the intravenous route is required because of patient factors preventing oral therapy, injection should be considered equivalent to infusion.

2.2 Intravenous versus Oral Administration

A randomized, two-way, crossover study of oral esomeprazole (40 mg once daily) or intravenous pantoprazole (40 mg once daily) conducted in 30 healthy volunteers showed that oral esomeprazole produced greater acid suppression than intravenous pantoprazole both on days 1 and 5 of treatment (pH >5.0: 28.7% vs 15.6%, and 45.5% vs 23.9% on day 1 and 5, respectively; $p < 0.001$ for both comparisons).[19]

Additionally, a study conducted in 19 critically ill patients receiving acid suppression to prevent stress ulcer mucosal damage found that, despite a lower bioavailability, enteral lansoprazole suppressed acid to a greater extent than intravenous lansoprazole (average pH over the first 24 hours 3.67 vs 2.89; $p = 0.03$).[20]

An interesting study compared lansoprazole administered after endoscopic haemostasis in patients with UGIH, either as an intravenous bolus plus constant infusion (90 mg bolus + 9 mg/h infusion for 72 hours, n = 32) or an oral bolus (120 mg, n = 34) followed by a 30-mg tablet every 3 hours (n = 34). This study showed that, despite a mean gastric pH at 1 hour that was significantly higher in the intravenous than in the oral group (5.3 ± 0.4 vs 3.3 ± 0.4, respectively; difference 2.0; 95% CI 0.8, 3.1; $p < 0.001$), there was no difference in the number of patients achieving the target intragastric pH (intragastric pH was >6 for 67.8% of the study period with the intravenous PPI and 64.8% with the oral PPI), although the achievement of pH >6 occurred 1 hour later in the oral group compared with the intravenous bolus group. This study suggests that frequent oral PPI administration may be able to replace the currently recommended intravenous bolus plus infusion PPI therapy in patients with bleeding ulcers, since neither mean proportion of time nor the number of patients with a pH value >4, 5 or 6 were different between both groups.[21] A previous study from the same group, although conducted in healthy volunteers, showed that oral high-dose lansoprazole was associated with insufficient control of gastric pH.[22] One explanation might be the higher proportion of *H. pylori*-positive patients in the former study (bleeding patients) than in the latter study (healthy volunteers). Finally, a small randomized, two-way, crossover, comparative study performed in healthy volunteers who received esomeprazole 40 mg as a 30-minute intravenous infusion or orally once-daily for 5 days, separated by a wash-out period of at least 13 days, demonstrated that both regimens provided similar levels of intragastric acid control on both day 1 and day 5 (figure 1).[14]

At that time, there were still some controversies surrounding the use of intravenous-PPIs in clinical situations where a fast and strong inhibition of acid secretion is needed, mainly

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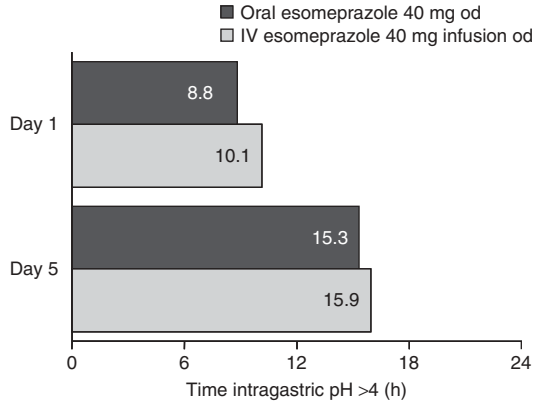

Fig. 1. Mean time with intragastric pH >4 over the 24-hour period on day 1 and day 5 after intravenous (IV) or oral administration of esomeprazole 40 mg once daily (od) in 38 healthy male and female volunteers (reproduced from Wilder-Smith et al.,[14] with permission).

acute peptic ulcer bleeding, and more studies are warranted to ascertain the best strategy.

2.3 Comparison of Gastric pH Control with Intravenous PPIs

Several studies[23-25] have compared acid control obtained with either esomeprazole or pantoprazole, and have suggested that intravenous esomeprazole provides an intragastric acid control that is faster and more pronounced than administration of pantoprazole (table I).

Intravenous esomeprazole was compared with intravenous lansoprazole in an open-label crossover study where healthy *H. pylori*-negative adults were randomized to one of two treatment sequences, each consisting of two 5-day dose administration periods of intravenous esomeprazole 40 mg or intravenous lansoprazole 30 mg. During the first 4 hours of pH monitoring, intragastric pH was >4.0 significantly longer on days 1 and 5 with esomeprazole than lansoprazole ($p < 0.0001$). Furthermore, median hours to stable pH >4.0 was significantly shorter for esomeprazole (4.92) than for lansoprazole (5.75).[26]

However, it is worth noting that these differences in pH control have not been proven to result in clinical superiority.

3. The Use of Intravenous PPIs in Managing Acute Upper Gastrointestinal Haemorrhage

Acute UGIH, defined as bleeding proximal to the ligament of Treitz, is a common and clinically important condition with significant healthcare cost implications worldwide. Common negative outcomes include rebleeding and mortality, with deaths secondary to decompensation of pre-existing co-morbid medical conditions precipitated by the acute bleeding event.

It is well known that management of such patients is based on a multidisciplinary approach (for review see Gralnek et al.[27]) and that the first step of treatment of the active lesion is based on endoscopic haemostasis.[6] Indeed, Leontiadis et al.[28] have shown that patients most likely to benefit from pharmacological management are those who have undergone endoscopic haemostasis.

Experimental data have shown that gastric acid impairs clot formation, promotes platelet disaggregation and stimulates fibrinolysis.[29]

Table I. Time with intragastric pH >4, expressed as a percentage of the different time periods (timepoint) according to the study design, following administration of intravenous esomeprazole 40 mg or intravenous pantoprazole 40 mg.

Study	Timepoint	Time with pH >4 (%)		p-Value
		esomeprazole	pantoprazole	
Wilder-Smith et al.[23]	Day 1	8.3	5.3	$p < 0.001$
	Day 5	13.9	9.0	$p < 0.0001$
Hartmann et al.[25]	24-h period	49.2	23.3	$p < 0.001$
	First 6 h	56.7	35.0	$p < 0.001$
Piccoli et al.[24]	Day 1	38.8	23.7	$p < 0.0001$
	Day 3	55.0	35.2	$p < 0.0001$

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Thus, increasing and maintaining gastric pH to 6 or more may decrease the risk of rebleeding by increasing clot stability.

The use of high-dose intravenous PPI (80 mg intravenous bolus followed by a 8 mg/hour constant infusion for up to 72 hours for omeprazole, pantoprazole and esomeprazole) in the management of UGIH is controversial, since studies from North America show that even a constant high-dose infusion of PPI may not be able to sustain an intragastric pH >6.[30]

Four randomized clinical studies that assessed the efficacy of high-dose intravenous omeprazole after endoscopic haemostasis in UGIH have been published.[31-34] In two, of these studies, omeprazole has been compared with placebo,[32,34] whereas for the other two, the comparator was a histamine H_2 receptor antagonist either alone[33] or in combination with somstostatin.[31] Although none of these studies alone were able to show a significant improvement in survival, a meta-analysis demonstrated that the use of high-dose intravenous omeprazole not only significantly reduced the rates of rebleeding and emergency surgery, but also improved survival.[4] This was confirmed in a recent meta-analysis showing that the use of PPIs decreased the risk of death (odds ratio [OR] 0.53; 95% CI 0.31, 0.91 in patients who had active bleeding or a non-bleeding visible vessel)[28] as well as by a 'real-world' setting registry showing that decreased rebleeding and mortality were significantly and independently associated with PPI use (OR 0.53; 95% CI 0.37, 0.77 for rebleeding; and OR 0.18; 95% CI 0.04, 0.80 for mortality).[35]

It has been suggested that because of underlying physiological differences with non-Asian patients, such as a high prevalence of slow metabolizers or of *H. pylori* infection, the beneficial effect of intravenous PPI might only be observed in Asian patients.[28]

One North American randomized controlled trial of intravenous high-dose pantoprazole versus the H_2-receptor antagonist ranitidine studied non-Asian patients experiencing acute bleeding from a peptic ulcer (n = 149). The study was stopped early because of slow enrolment and, despite a numerical trend (52% risk reduction) in favour of pantoprazole, statistical significance was not achieved (rebleeding rate 6.9% vs 14.3% for pantoprazole and ranitidine, respectively; OR 0.48; 95% CI 0.18, 1.33; p = 0.19). Furthermore, no trend was observed for reduced mortality (30 days mortality 4% in both groups).[36]

A randomized, placebo-controlled study conducted in India (i.e. including Asian patients) was published the same year and, despite a small sample size (102 and 101 patients for the pantoprazole and placebo arms, respectively), this study concluded that pantoprazole administered as a constant infusion (80 mg bolus plus 8 mg/hour infusion for 72 hours) after dual endoscopic haemostasis reduced rebleeding, transfusion requirements and hospital stay with a numerical trend towards a reduced mortality.[37]

More recently, a study was published presenting the results of a randomized double-blind comparison of pantoprazole (40 mg intravenous bolus followed by a 8 mg/hour constant infusion) and somatostatin (250 mg bolus followed by a 250 mg/hour constant infusion) both for up to 48 hours.[38] The study was conducted in Greece and thus is likely to have included a vast majority of non-Asian patients. The risk of rebleeding was significantly reduced by pantoprazole compared with somatostatin (OR 0.29; 95% CI 0.1, 0.83); however, neither the need for urgent surgery nor the mortality rates were different between both groups. Interestingly, neither the time spent above a pH value of 6 (81.5% vs 82.9% for pantoprazole and somatostatin, respectively) nor the median 24-hour pH values (6.03 vs 6.02) were different between groups.

A large, randomized, double-blind study compared pantoprazole (n = 625) with ranitidine (n = 631) in patients with UGIH was presented in 2004,[39] although it was never published as a full article. This study had a major methodological issue in allowing the use of routine second-look endoscopy (which is not recommended)[27] and this did not allow adoption of traditional outcomes. Nevertheless, this study did not show any benefit for pantoprazole over ranitidine.

Intravenous esomeprazole (80 mg bolus infusion over 30 minutes followed by 8 mg/hour for 71.5 hours) was assessed very recently in a large,

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randomized, double-blind, placebo-controlled trial evaluating its effects in high-risk patients who have undergone endoscopic haemostasis for peptic ulcer bleeding.[40] The vast majority of participants were non-Asian patients (87%, 667 of 764) and found that, compared with placebo (n = 389), esomeprazole (n = 375) reduced by 43% the risk of rebleeding both within the first 72 hours and the first 30 days (OR 0.57; 95% CI 0.35, 0.94; and OR 0.57; 95% CI 0.37, 0.87, respectively). Despite a positive trend in favour of esomeprazole (OR 0.39; 95% CI 0.10, 1.47), this study was underpowered to show a significant decrease in 30-day mortality.

Controversially, a study published at the end of 2008 compared an intensive regimen (80 mg bolus followed by 8 mg/hour as continuous infusion for 72 hours) with a standard regimen (40 mg bolus daily followed by saline infusion for 72 hours) of either omeprazole or pantoprazole used after endoscopic haemostasis for peptic ulcer haemorrhage.[41] This study, which included 474 patients, suggested that standard-dose PPIs infusion was as effective as a high-dose regimen in reducing the risk of recurrent bleeding. Despite methodological limitations such as scheduled second-look endoscopy used to define recurrent bleeding in some patients, this study strongly questions the high-dose regimen PPI that is currently recommended.

The use of intravenous PPI in patients waiting for endoscopy is a matter of debate. A meta-analysis that included four randomized clinical trials and 1512 patients was published in 2006 that found no statistically significant differences in rates of mortality, rebleeding or surgery between PPI and control treatment.[42] Nevertheless, this meta-analysis found that PPI treatment compared with control significantly reduced the proportion of patients with stigmata of recent haemorrhage at the time of endoscopy, and the wide confidence intervals for the clinical outcomes in the meta-analysis do not rule out the possibility of clinically relevant differences.[42]

A more recently published randomized placebo-controlled clinical trial conducted in Hong Kong that included 638 patients found similar results with an additional benefit in the use of pre-endoscopic PPIs in terms of proportion of patients requiring subsequent endoscopic haemostasis (19.1% vs 28.4%; p = 0.007) and of length of hospital stay (<3 days in 60.5% and 49.2%; p = 0.005).[43]

Therefore, to summarize the clinical studies that have assessed efficacy of intravenous PPIs in peptic ulcer bleeding, it appears that these drugs are more efficacious than placebo for reducing risk of rebleeding and surgery. It has only been suggested from several meta-analyses that they can also decrease mortality in high-risk patients who have undergone endoscopic haemostasis.[4,28] It is of interest to note that meta-regression analysis performed by Leontiadis et al.[28] did not show an association between the route of PPI administration (intravenous or oral) with treatment effect (mortality, rebleeding or surgical intervention), suggesting that there is no proven difference in clinical outcome between routes of administration at this time. Further studies of adequate power are encouraged to delineate the optimal dose and route for PPIs.

Cost effectiveness is also important, especially from a regulatory or healthcare system perspective. A few years ago, we published a decision-tree analysis suggesting that, in the USA and Canada, administration of a high-dose intravenous PPI for 3 days is both more effective and less costly than not doing so for patients with bleeding ulcers after successful endoscopic haemostasis.[5] It has also been suggested that the use of intravenous PPI before endoscopy in patients presenting with acute UGIH may also be a cost-effective option despite remaining uncertainties surrounding its clinical efficacy because existing data is from insufficiently powered clinical trials.[44,45]

To date, no head-to-head comparisons of intravenous PPIs have been performed in patients with peptic ulcer bleeding, and thus there is no definitive evidence to recommend any one PPI over another. Omeprazole is the PPI that has been the more frequently assessed in randomized trials, although pantoprazole has also been studied in recent randomized trials, and esomeprazole was the first to show a beneficial effect in a population not restricted to Asian patients. Decision makers may wish to select the PPI

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based on the preponderance of evidence in their relevant population, and also based on local availability and costs.

4. The Use of Intravenous PPIs in Erosive Oesophagitis

Reflux oesophagitis is a common disease, with erosive reflux oesophagitis being a more advanced stage of reflux oesophagitis. Although death from reflux disease is uncommon, significant morbidity and mortality from complications, such as oesophageal ulcer, stricture and cancer, are not uncommon. GORD is a very common condition since some 20–40% of the population in the Western world experience heartburn, which is the principal symptom of GORD.[46] Furthermore, many hospitalized patients have GORD as a concomitant condition and hospitalized patients who spend long periods supine are at greater risk of developing GORD.[47]

The standard of pharmacological management for patients with erosive oesophagitis is the use of oral PPIs because it has been demonstrated that there is a direct relationship between healing of the oesophagus and time with an intragastric pH >4;[12] nevertheless, sometimes patients are unable to swallow or to absorb oral PPIs, for example, in the case of short bowel syndrome.

Unfortunately, there are few studies assessing the efficacy of intravenous PPIs in erosive oesophagitis, and none that directly compare two or more PPIs with each other.

A study conducted in patients with endoscopically proven oesophagitis compared the efficacy of three regimens of esomeprazole 40 mg/day (i.e. via a 3-minute injection, a 30-minute infusion or orally for 1 week), followed by 3 weeks of open-label treatment with oral esomeprazole 40 mg/day and found similar healing rates at 4 weeks for the three regimens, injection plus oral 79.7%; infusion plus oral 80.2% and oral alone 82.6%, suggesting that both intravenous and oral routes, and intravenous injection and infusion were equivalent in efficacy.[18]

Intravenous pantoprazole 40 mg once daily was compared with the same dose of oral pantoprazole in a 7-day randomized, double-blind, parallel-group, placebo-controlled study in 78 patients (n = 26 intravenous, 27 oral and 25 placebo) with GORD and a history of erosive oesophagitis. At 7 days, maximal (mean values, 8.4, 6.3 and 20.9 mEq/hour for intravenous and oral pantoprazole and placebo, respectively) and basal acid output were significantly lower with pantoprazole than with placebo ($p < 0.001$), and there was a numerical trend towards improved GORD symptoms and antacid usage.[48]

More recently, a very small study (six patients in each treatment arm) compared two regimens for pantoprazole administration in patients with ulcerative oesophagitis. Patients were randomized to receive either intravenous pantoprazole 80 mg bolus then 8 mg/hour infusion for 72 hours, then 40 mg orally once a day for 4 days (group A) or 40 mg pantoprazole intravenously once a day for 72 hours, then orally once a day for 4 days (group B). A second endoscopic examination was performed at the end of first week of treatment and revealed that severe erosive oesophagitis healed completely in three patients and significantly in the other three in group A, whereas it only partially healed in five patients in group B by the time of second endoscopy ($p = 0.015$). This study supports the use of high-dose constant infusion of pantoprazole in the treatment of severe oesophagitis because oesophagitis can be completely healed in a few days.[49]

Thus, it seems reasonable to recommend the use of an intravenous PPI for patients with GORD and erosive oesophagitis who are not able to receive their medication by mouth. At this time, it is not possible to rank the different PPIs administered intravenously for this indication because of the lack of head-to-head comparisons. Nevertheless, a meta-analysis compared healing obtained with standard doses of oral PPIs in the short-term management of GORD with erosive oesophagitis and found no difference between omeprazole and rabeprazole (relative risk [RR] 0.92; 95% CI 0.52, 1.62), between omeprazole and lansoprazole (RR 1.10; 95% CI 0.88, 1.38), between omeprazole and pantoprazole (RR 1.00; 95% CI 0.80, 1.25) and between lansoprazole and pantoprazole (RR 0.95; 95% CI 0.65, 1.38).[50] In contrast, the risk of not being healed at 4 weeks

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was found to be higher with omeprazole than with esomeprazole (RR 1.19; 95% CI 1.02, 1.39), with a number needed to treat for one additional healed oesophagitis of 17 (95% CI 9, 100). Nevertheless, it is noticeable that some studies comparing oral PPIs have suggested they might not all be considered equivalent in the healing of erosive oesophagitis. For example, the very large study (>5000 patients) published by Castell et al.[51] showed that esomeprazole was superior to lansoprazole for healing rates of erosive oesophagitis and, more interestingly, that the beneficial effect increased with the severity of the oesophagitis.

More recently, esomeprazole was compared with pantoprazole (both at 40 mg once daily) in a randomized, single-blind study among patients diagnosed with endoscopically proven GORD. This study suggested that healing is faster with esomeprazole than with pantoprazole (at 4 weeks healing rates were 77.8% vs 72.2%, respectively), but that healing rates at 8 weeks and proportion of heartburn-free days were similar in both groups of patients.[52] It has also been suggested that esomeprazole 40 mg provides greater acid control in more patients and maintains intragastric pH >4 for a longer period than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with symptoms of GORD.[53]

5. Use of Intravenous PPIs in Preventing Stress-Induced Mucosal Damage

UGIH as a result of stress ulceration remains an important complication in critically ill patients,[54] although the prevalence of the disease has decreased during the past two decades and controversy remains regarding the need for routine prophylaxis of stress ulceration. Bleeding tends to be associated with prolonged hospital stay and is more likely to occur in patients with more severe underlying illnesses, with duodenal ulcer disease as the most common source of this bleeding.[55] Prophylaxis against stress ulcers, with measures such as neutralization of gastric acid, reduction of gastric acid secretion or cytoprotection, has traditionally been recommended for the prevention of UGIH in critically ill patients with known risk factors (respiratory failure and coagulopathy).[56] Since their development, PPIs have become popular for many clinicians as agents for preventing GI bleeding in critical care settings. PPIs have greater pharmacological efficacy than H_2-receptor antagonists, as indicated by both the degree and duration of pH elevation they induce. In addition, the development of thrombocytopenia, a well documented complication of H_2-receptor antagonist use, is rarely associated with the use of PPIs. Despite these theoretical advantages of PPIs, few data are available to compare the effectiveness of this class of drug with the effectiveness of H_2-receptor antagonists in the clinical setting.

A prospective, randomized trial published >10 years ago compared intravenous ranitidine 150 mg daily (n = 35) with omeprazole 40 mg daily (n = 32) administered orally or via the nasogastric route.[57] Baseline characteristics of the two groups were similar except for the number of risk factors per patient, 2.7 versus 1.9 for the ranitidine and omeprazole groups, respectively ($p < 0.05$). Eleven patients (31%) receiving ranitidine and two patients (6%) receiving omeprazole developed clinically important bleeding ($p < 0.05$). Authors from this study concluded that oral omeprazole is safe, effective and clinically feasible for stress ulcer prophylaxis, but it has to be noted that the incidence of the disease was very high in the ranitidine group. Indeed, in a non-inferiority trial comparing omeprazole immediate release orally or by nasogastric route (40 mg twice a day and 40 mg each day thereafter) with cimetidine (300 mg intravenous bolus followed by 50 mg/hour constant infusion), the rate of clinically significant bleeding in the per-protocol population was 4.5% with omeprazole suspension and 6.8% with cimetidine meeting the criteria for the non inferiority of omeprazole suspension.[58] Omeprazole immediate release was thus approved by the US FDA for this indication.

Faisy et al.[59] retrospectively compared 736 high-risk patients who received stress prophylaxis with either sucralfate or ranitidine (January 1996 to March 1997) to 737 patients (April 1997 to June 1998) who did not. The rate of overt UGIH

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was the same in both cohorts (1.9% and 1.6%, respectively), suggesting that the incidence of the disease is very low and that treatment with sucralfate or ranitidine has no significant impact on it.

There is only one published study that has assessed the efficacy of intravenous omeprazole in stress-induced mucosal damage, in a randomized, fomotidine-, sulcralfate- and placebo-controlled trial.[9] This study included 287 patients with high risk for stress-related UGIH after a trauma or major surgery. This study did not show that omeprazole, famotidine or sucralfate prophylaxis reduced the incidence of clinically important stress-related bleeding because the incidence was already very low in control patients. Indeed, clinically significant stress-related UGIH was observed in 1%, 3%, 4% and 1% of patients assigned to receive omeprazole, famotidine, sucralfate and placebo, respectively ($p > 0.28$).

More recently, a database evaluation of high-risk patients receiving either the H_2-receptor antagonist famotidine ($n = 522$) or pantoprazole ($n = 95$) intravenously found that UGIH was more frequent in the pantoprazole than in the famotidine group (3.2% vs 0.38%; OR 8.48; 95% CI 1.40, 51.48; $p = 0.028$).[60] These authors had no formal explanation for this difference; however, they suggest a channelling bias with a propensity to use PPIs in sicker patients because PPIs are perceived as more effective agents, although most patients received the H_2-receptor antagonists.

In a prospective, multicentre pilot study, intravenous pantoprazole was compared with intravenous cimetidine in the management of 202 critically ill patients at risk for stress-related mucosal damage.[61] Patients were randomized to either intravenous pantoprazole 40 mg every 12 or 24 hours; intravenous pantoprazole 80 mg every 8, 12 or 24 hours; or intravenous cimetidine 300 mg bolus followed by a 50 mg/hour infusion. On day 1, the cimetidine infusion resulted in a pH ≥4.0 for 82% of the time, whereas the pantoprazole regimens resulted in a pH ≥4.0 for <70% of the time. On day 2, the percentage of time at pH ≥4.0 decreased to 77% with cimetidine, possibly as a result of the rapid development of tolerance. In contrast, the duration of targeted pH level increased with all the pantoprazole regimens. Pantoprazole 40 mg twice daily and 80 mg twice daily provided comparable results with a pH ≥4.0 for 73% and 77% of the time, respectively, and pantoprazole 80 mg three times daily surpassed cimetidine by maintaining pH ≥4.0 for 86% of the time. It was concluded that intermittent pantoprazole was effective in maintaining the desired intragastric pH to provide adequate stress ulcer prophylaxis in critically ill patients, and that both drugs might be effective since there were no cases of protocol defined UGIH bleeding in any treatment group.[61]

In summary, the burden of the disease is vague and the risk of clinically important bleeding has decreased during the past decade independently of the use of prophylaxis.[9,59,62] There are no strong data supporting the benefit of any one class of drug (PPIs, H_2-receptor antagonists or sucralfate) over the other, and when a PPI is being used, there are no data to support the choice of either a specific molecule or dosage. Furthermore, prophylaxis against stress ulcers might significantly impact health resources since it is expensive, and about two-thirds of intravenous prescriptions for acid-suppressive agents in the US were reported to be for stress ulcer and acid aspiration prophylaxis, rather than for the more definitively proven effective and cost-effective indication of treatment for peptic ulcer bleeding.[1] Additionally, stress ulcer prophylaxis may cause adverse effects such as nosocomial pneumonia[9] or *Clostridium difficile* diarrhoea,[63,64] although this is a controversial issue. Thus, routine prophylaxis for patients entering the medical intensive care unit does not seem warranted given the available evidence; in addition, there is a real need for a more rational use of intravenous PPI in intensive care patients since a retrospective analysis of 43 patients receiving intravenous PPIs for stress ulcer prophylaxis found that none of the patients had an appropriate indication for pantoprazole.[59]

6. Safety Issues Raised by the Use of Intravenous PPIs

Several safety issues have been raised with either long-term use of PPIs or the use of high-dose

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PPI therapy. Nevertheless, these adverse events are unlikely to outweigh the outstanding therapeutic benefits of PPIs when they are appropriately prescribed.

6.1 Community-Acquired Pneumonia

The risk of community-acquired pneumonia (CAP) is related to gastric bacterial overgrowth when the gastric pH increases. However, there are no strong data supporting this assumption. Indeed, a recently published case (n = 80 066) control (n = 799 881) study found that overall the use of PPIs was not associated with CAP, requiring hospitalization or not, (adjusted OR 1.01; 95% CI 0.91, 1.12; and adjusted OR 1.02; 95% CI 0.97, 1.08, respectively), whereas there was a strong increase in risk for CAP associated with current use of PPI therapy that was started within the previous 2 days (adjusted OR 6.53; 95% CI 3.95, 10.80), 7 days (adjusted OR 3.79; 95% CI 2.66, 5.42) and 14 days (adjusted OR 3.21; 95% CI 2.46, 4.18).[65] These findings were consistent with those of a previously published case control study.[66] On the other hand, a review of 31 clinical trials, in which 16 583 patients received esomeprazole and 12 044 patients received either placebo or comparator acid-suppressive drugs, found no causal association between acid-suppressive therapy with esomeprazole and increased risk of community-acquired respiratory tract infections, including pneumonia, in patients receiving this agent for gastric acid-related disorders.[67]

6.2 Bone Loss and Fractures

Some studies have described an increased risk for bone fracture in patients using PPIs. The mechanisms underlying this effect are that PPIs could impair intestinal calcium absorption and inhibit the bone proton pump. Recent studies have lead to controversial conclusions, with some suggesting that PPI use may be associated with a modestly increased risk of nonspine,[68] hip[69] or vertebral fracture in older women and perhaps older men with low calcium intake;[70] whereas another study published the same year concluded that the use of PPIs does not increase the risk of hip fracture in patients without major risk factors.[71] If the risk exists, it appears to be restricted to very long-term (>7 years) users.

6.3 *Clostridium difficile* Infection

Recent reports suggest an increasing occurrence and severity of *C. difficile*-associated disease. A population-based, case-control study showed that current use of PPIs increased the risk of *C. difficile*-associated disease almost by 3-fold (OR 2.9; 95% CI 2.4, 3.4).[63]

7. Conclusions

Intravenous administration of PPIs remains a useful route when patients cannot take oral therapy for any valid reason or for any patient with acute UGIH when high-dose therapy is warranted. Intravenous administration of PPI may be a faster way to achieve gastric acid suppression than oral administration of the same agent, although the clinical relevance of the speed of acid suppression remains unproven for most conditions. Peak suppression after intravenous high-dose administration occurs within hours, compared with several days later after oral administration at recommended dosages. Each intravenous PPI formulation has been approved for different indications; the key differences between them relate to their ability to reach specific gastric pH, time to maintain a specific gastric pH and ease of use of the intravenous formulation. Whether any of these differences translate to important clinical differences remains to be proven because they have not been compared head-to-head in clinical trials. Some of the proposed indications remain controversial (i.e. stress ulcer prophylaxis) and there is a weak body of evidence to support the use of a specific molecule over another. One rule might be to reason not on a class-effect basis, or to use the drug that is approved in a specific indication such as GORD or UGIH. The treatment cost has to be weighed against the cost of an event that could have been avoided, such as one episode of rebleeding, to have an adequate evaluation of the cost-effectiveness of the drug.

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