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A clinical guide to using intravenous proton-pump inhibitors in reflux and peptic ulcers

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***Abstract*:** Intravenous (IV) proton-pump inhibitors (PPIs) are potent gastric acid suppressing agents, and their use is popular in clinical practice. Both IV and oral PPIs have similarly short half-lives, and their effects on acid secretion are similar, thus their dosing and dosage intervals appear to be interchangeable. The possible exception is when sustained high pHs are required to promote clot stabilization in bleeding peptic ulcers. Continuous infusion appears to be the only form of administration that reliably achieves these high target pHs. IV PPI is indicated in the treatment of high-risk peptic ulcers, complicated gastroesophageal reflux, stress-induced ulcer prophylaxis, Zollinger–Ellison syndrome, and whenever it is impossible or impractical to give oral therapy. The widespread use of PPIs has been controversial. IV PPIs have been linked to the development of nosocomial pneumonia in the intensive care setting and to spontaneous bacterial peritonitis in cirrhotic patients. This review discusses the use of IV PPI in different clinical scenarios, its controversies, and issues of appropriate use.

***Keywords*:** proton-pump inhibitor (PPI), H2-receptor antagonist, acid secretion, peptic ulcer, gastroesophageal reflux disease, stress ulcer, bleeding ulcer, gastrointestinal hemorrhage, Zollinger-Ellison syndrome

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Introduction

The introduction of the first proton-pump inhibitor (PPI), omeprazole, in 1989, marked the end of a search for effective control of acid secretion. Omeprazole was followed by lansoprazole (1995), pantoprazole (1997), rabeprazole (1999), and the S-enantiomer of omeprazole, esomeprazole (2001). PPIs are available in intravenous (IV) and oral forms (enteric-coated delayed release, microencapsulated beads in a capsule or suspension, and unprotected drug with sodium bicarbonate).

Currently, IV PPI is approved by the US Food and Drug Administration (FDA) for treating patients who are unable to tolerate oral medications due to complicated erosive esophagitis, and in patients with Zollinger–Ellison syndrome (ZES) with pathological hypersecretory states. In real life practices, the use of IV PPI is much more widespread. The decision to administer IV PPI depends on several factors such as the ability of the patient to swallow, gastric motility, intestinal transport and permeability, and cytochrome p450 activity. These factors often come into play in critically ill patients, who may require IV PPIs either to treat acid-secreting disorders, or as prophylaxis against stress-related mucosal injury. IV PPI plays a synergistic role in the treatment of bleeding peptic ulcers requiring endoscopic hemostasis, although its cost-effectiveness requires further study.

The widespread use of IV PPI has caused controversy, including concern over its association with respiratory complications in the critically ill, and with spontaneous bacterial peritonitis (SBP) in cirrhotic patients. IV PPIs have been reported to be commonly used inappropriately which, if true, represent a misuse of healthcare resources. This article reviews the current evidence for the use of IV PPIs in peptic ulcer disease and gastroesophageal reflux disease (GERD), including the controversies, and also addresses issues surrounding appropriate use.

Pharmacology – overview

PPIs are substituted benzimidazoles that covalently bind to the H^+/K^+ ATPase enzyme,

selectively and irreversibly inhibiting this final step of acid secretion in a dose-dependent manner [Richardson *et al.* 1998]. PPIs are more potent than histamine H2-receptor antagonists (H2RAs), which only inhibit one of the pathways involved in acid secretion. With prolonged dosing, tolerance to the antisecretory effect of H2RAs develops [Merki and Wilder-Smith, 1994]; this does not occur with PPIs. Thus, PPIs have become the drug of choice when potent inhibition of acid-secretion is required.

Currently, three IV PPIs are available in the US (esomeprazole, pantoprazole and lanzoprazole). IV omeprazole is available in Europe and Asia. IV PPIs should be administered through a dedicated IV line, and flushed with compatible solutions pre- and post-administration [Package inserts (Prevacid, Protonix, Nexium), 2009]. They should not be administered concomitantly with other medications. Esomeprazole and pantoprazole may be administered as a bolus (over 3 min and 2 min, respectively) or as an IV infusion (over 10–30 min and 15 min, respectively) [Protonix, Nexium (package insert), 2009]. Lansoprazole is approved for IV infusion over 30 min only and requires administration through a 1.2 μm pore size in-line filter to remove any precipitate that may form when the reconstituted drug product is mixed with IV solutions [Package insert (Prevacid), 2009]. Esomeprazole and pantoprazole do not require a filter for administration.

PPIs are predominantly inactivated by the 2C19 and 3A isoform of the hepatic cytochrome p450 (CYP) mixed function oxidase system; the metabolites are then eliminated in the urine and feces. The CYP2C19 gene located on chromosome 10 displays genetic polymorphism, with three common inactivating mutations. Individuals with two mutant CYP2C19 alleles (poor metabolizers) metabolize PPIs more slowly than those with one mutant or two wild-type alleles (extensive metabolizers). Poor metabolizers may display a greater response to a standard dose of PPI compared with extensive metabolizers [Sugimoto *et al.* 2006; Sagar *et al.* 2000]. The prevalence of CYP2C19 mutations is more prevalent in Asian populations (13–23%), compared with European and North American white populations (3–5%) [Furuta *et al.* 2005, 1998]. This results in a higher plasma level of PPI in Asians, and may in part explain the improved efficacies of PPI seen in this population, especially considering the higher prevalence of *Helicobacter pylori*, and decreased gastric parietal cell mass in Asians.

Use of intravenous PPI in peptic ulcer disease

The use of IV PPI is perhaps best established in the treatment of complicated peptic ulcer disease, and has largely replaced the use of H2RA. A meta-analysis of 24 randomized controlled trials with 4373 patients, comparing IV or oral PPI with placebo or H2RA in bleeding peptic ulcers, reported that PPI treatment in peptic ulcer bleeding reduces rebleeding and surgery compared with placebo or H2RA [Leontiadis *et al.* 2006]. All-cause mortality was not affected.

Intragastric pH studies – oral *versus* intravenous PPI

Endoscopic hemostasis plays a pivotal role in the treatment of bleeding peptic ulcers, and although this is successful >90% of the time, rebleeding still occurs within 72 h in up to 25% of cases [Laine and Peterson, 1994]. *In vitro*, an intragastric pH of >6 has been shown to promote clot stabilization by reducing pepsin-induced clot lysis and increasing platelet aggregation [Barkun *et al.* 1999]. It follows that rapid achievement and maintenance of an intragastric pH of >6 theoretically provide the optimal environment for peptic ulcer healing and clot stabilization to occur.

Several studies have looked at the efficacy of PPIs, given in a combination of oral, IV bolus (defined as administration with an IV push at regular intervals) and high dose IV continuous infusion forms (usually preceded by an 80 mg bolus IV push, followed by an infusion at 8 mg/h), in achieving and maintaining this pH target goal of >6 [Javid *et al.* 2009; Laine *et al.* 2008; Hartmann *et al.* 1998]. Theoretically, high-dose IV continuous infusion should provide the most potent acid suppression. PPIs only inhibit stimulated parietal cells with active proton pumps and this is most successfully and rapidly achieved by administering a bolus dose intravenously (providing 100% bioavailability theoretically); continuous infusion then provides a steady state of the drug to inactivate any newly synthesized proton pumps, as well as any newly recruited proton pumps on parietal cells [Welage *et al.* 2003], which continue to be stimulated by gastrin, histamine and food.

However, this theoretical superiority has not been borne out as strongly in the medical literature as one may have expected. In one study, oral and IV pantoprazole were equipotent in raising

intragastric pH, when administered at the same dose and intervals [Hartmann *et al.* 1998]. In another intragastric pH study on 90 patients, who had received endoscopic therapy for a bleeding peptic ulcer, infusional IV was compared against the oral forms of omeprazole, pantoprazole and rabeprazole [Javid *et al.* 2009]. All groups achieved a mean 72 h intragastric pH of >6, and there were no significant differences between the oral and infusional IV arms of each drug. Similar results were obtained with infusional IV and oral lansoprazole, although IV lansoprazole was more rapid in raising intragastric pH initially [Laine *et al.* 2008].

The debate between infusional IV and oral PPI becomes more complicated when one wonders whether achieving an intragastric pH of >6 is truly a key variable. Some intragastric pH studies reported achieving a pH of >6 less than 30% of the time with infusional IV PPI [Metz *et al.* 2006]. The solution to this could lie in the addition of a buffering agent; for example, sodium bicarbonate, to a PPI. Sodium bicarbonate has already been shown independently to have the ability to raise intragastric pH [Lin *et al.* 1998; Simmons *et al.* 1986]. This combination should allow high intragastric pHs to be easily and reliably achieved [Julapalli and Graham, 2005]. However, no trials to date have shown that upper gastrointestinal hemorrhage (UGIH) patients have higher rebleeding rates if an intragastric pH of >6 is not continuously maintained. It remains unclear whether this theoretical goal is indeed clinically relevant.

Post-endoscopic intravenous PPI

IV PPI infusion, in combination with endoscopic hemostasis, has been shown to achieve the lowest rebleeding rates in ulcers with high risk bleeding stigmata [Zargar *et al.* 2006; Lau *et al.* 2000]. In a landmark study by Lau *et al.* [2000], patients who underwent successful endoscopic hemostasis of peptic ulcers with high risk stigmata, were subsequently randomized to receive either 80 mg bolus of IV omeprazole followed by a continuous infusion of 8 mg/h for 72 h, or a bolus followed by a placebo infusion. Patients who received the high dose PPI infusion had significantly lower rebleeding rates, when compared to those who received a placebo (6.7% *versus* 22.5%, $p < 0.001$). The importance of endoscopic hemostasis, in combination with high dose IV PPI, was reinforced in a study by Sung *et al.* [2003], in which patients with ulcers with nonbleeding visible vessels and clots were randomized to infusional IV omeprazole alone, or to endoscopic hemostasis first, followed by infusional IV omeprazole. Patients receiving the combination treatment had significantly lower rebleeding rates compared to those who received infusional IV omeprazole alone (1.1% *versus* 11.6%, $p = 0.009$).

Although the use of IV PPI postendoscopic hemostasis has now become standard of care, the above studies have limitations of being single center reports, consisting mainly of Southeast Asians. The apparent efficacy of this approach has been challenged by studies with inconsistent conclusions in Western Europe and North America [Jensen *et al.* 2006; Hasselgren *et al.* 1997; Schaffalitzky de Muckadell *et al.* 1997]. Moreover, mortality (probably the most important clinical outcome) has never been shown to be affected by the use of IV PPI. Racial differences in genetic polymorphisms of the CYP450 system, parietal cell mass and the prevalence of *Helicobacter pylori* have challenged the external validity of the efficacy of high-dose infusional IV PPI. This controversy appears to have been laid to rest with a recent randomized, double-blinded, placebo-controlled trial by the Peptic Ulcer Bleed Study Group, consisting of 767 patients (mainly Caucasians) from 16 countries [Sung *et al.* 2009]. This study reinforced the efficacy of IV PPI infusion postendoscopic hemostasis (5.9% rebleeding within 72 hours in the IV esomeprazole infusion bolus group *versus* 10.3% in the placebo group; $p = 0.026$). The difference remained signficant at 7 and 30 days, suggesting that the benefits of the drug is unlikely race-specific, and appears to be unequivocal, when compared to placebo.

The conventional dosage of infusional IV PPI (80 mg bolus followed by 8 mg/h for 72 h), used in several studies [Sung *et al.* 2009; Zargar *et al.* 2006; Sung *et al.* 2003; Lau *et al.* 2000] and endorsed by consensus statements [Barkun *et al.* 2003; British Society of Gastroenterology Endoscopy Committee, 2002] have been challenged by studies which have found no difference between high dosage and low dosage IV PPI. Andruilli *et al.* [2008] conducted a study across 11 Italian centers, and found no difference in in-hospital rebleeding and overall mortality rates, in patients who were given the conventional high dose PPI infusion, compared with those who had a standard dose of 40 mg IV daily for 72 h [Andriulli *et al.* 2008]. This study had a few limitations. Firstly, only inhospital rebleeding rates were reported as opposed to the more conventional

28-day rebleeding rates. Patients who received the lower PPI dose had shorter hospital stays; post-discharge rebleeding episodes may have gone undetected in this group. Other similar investigations of PPI dosages have yielded conflicting results [Bajaj *et al.* 2007; Lin *et al.* 2006; Udd *et al.* 2001]. Large, prospective studies looking at hard clinical outcomes such as rebleeding rates and mortality are needed, before any recommendations can be made regarding the use of lower doses of IV PPI in bleeding peptic ulcers. A prospective study by Sung *et al.* is currently underway to clinically compare infusional IV and oral PPI in the postendoscopic hemostasis setting, the results of which will hopefully further clarify the picture.

Box 1. Summary of post-endoscopic intravenous PPI in peptic ulcer disease.

- PPIs are superior to H2RAs in reducing rebleeding and surgery in patients with bleeding peptic ulcers, but all cause mortality is not affected.
- Infusional IV, bolus IV and oral PPI, when given at the same dosage and intervals, are probably equipotent in raising intragastric pH. Infusional IV PPI likely achieves this fastest, although PPI plus antacid (e.g. sodium bicarbonate) would likely be even faster.
- Clinically, infusional IV PPI (80 mg IV bolus followed by 8 mg/h for 72 h), in combination with endoscopic hemostasis provides the lowest rebleeding rates in high-risk peptic ulcers.
- IV bolus and oral PPI may be as efficacious as infusional IV PPI, but more data is needed before this can be recommended.

PPIs, proton-pump inhibitors; H2RAs, H2-receptor antagonists; IV, intravenous.

Pre-endoscopic intravenous PPI

The next logical question is whether IV PPI given pre-endoscopically in patients with bleeding peptic ulcers would further improve patient outcomes. Daneshmend *et al.* [1992] first studied the pre-endoscopic use of omeprazole (IV bolus followed by intermittent IV and oral PPI) in 1992 in 1147 patients with UGIH, and reported a significant decrease in endoscopic signs of hemorrhage in patients who received omeprazole (33% omeprazole *versus* 45% placebo, $p = 0.0001$) [Daneshmend *et al.* 1992]. Similar findings were reported in a study by Lau *et al.* in 2007, which randomized 638 patients with UGIH to receiving either a high dose IV omeprazole infusion or a placebo prior to receiving an esophagogastroduodenoscopy (EGD) the following morning [Lau *et al.* 2007]. The need for endoscopic therapy was lower in the omeprazole group compared with the placebo group (19.1% *versus* 28.4%, $p = 0.007$), suggesting that high dose PPI infusion may hasten the resolution of bleeding stigmata and the healing of the bleeding lesions. Patients in the omeprazole group had shorter hospital stays, but there were no differences in 30-day rebleeding rates, need for surgery, or 30-day mortality. This could possibly be attributed to the use of IV PPI infusion post-endoscopic hemostasis, which may have reduced the rates of the aforementioned clinical outcomes to such a point, that small differences could no longer be detected even with their relatively large sample size. Although high dose IV PPI in stable patients waiting for an EGD appears to accelerate the healing of bleeding lesions and reduce the need for endoscopic therapy, it should not replace early endoscopy and prompt resuscitation, which remain vital in preventing adverse outcomes in patients with UGIH.

Box 2. Summary of pre-endoscopic IV PPI use.

- Pre-emptive infusional IV PPI in patients presenting with peptic ulcer bleeding may reduce the severity of bleeding stigmata and the need for endoscopic therapy.
- This should not replace prompt resuscitation and early EGD, especially in unstable patients.

IV, intravenous; PPIs, proton-pump inhibitors; EGD, esophagogastroduodenoscopy

Intravenous PPI in peptic ulcers with adherent clots

The approach towards a clot is controversial. The important factors to consider include the size of the clot, the location of the lesion, the likelihood of provoking massive bleeding, and the experience of the endoscopist. Reports varied in their vigor in clot irrigation before declaring clots adherent. Some use focal irrigation with a large thermal probe for up to 5 min; others use a mechanical device such as a snare to 'cheesewire' the clot. Some experienced endoscopists advocate treating such lesions with the clot *in situ* by slipping a hemostatic device under the clot, and treating the potential lesion blindly, with or without pretreatment with epinephrine injection. The clot becomes attached to the device and comes off when it is removed, and any residual lesion is then treated. A meta-analysis of six studies involving 240 patients favored clot removal by focal irrigation or by

the 'guillotine-snare' technique, and treating the underlying lesion endoscopically [Kahi *et al.* 2005]. Whether a clot should be removed or not remains controversial, especially when powerful PPIs are available. Laine *et al.* [1996] showed that after targeted irrigation for 5 min with a 3.2 mm heater probe, only 8% of tightly adherent clots rebleed. This rate is likely to be even lower if infusional IV PPI were given.

Box 3. Summary of IV PPI in peptic ulcers with adherent clots.

- The best approach for adherent clots remains unclear.
- Factors such as the size of the clot, location of the ulcer, likelihood of provoking massive bleeding and the experience of the endoscopist should be taken into consideration.

Cost-effectiveness of intravenous PPI in bleeding peptic ulcers

In the postendoscopic hemostasis setting, the administration of IV PPI has been shown to be more cost-effective than giving oral PPI, which in turn dominates over giving a placebo [Barkun *et al.* 2004a; Barkun *et al.* 2004b]. Another single center study compared the strategies of oral and IV PPI, in the context of performing diagnostic or therapeutic endoscopies in patients requiring hospitalization with acute peptic ulcer bleeding, and reported high dose IV PPI with therapeutic endoscopy to be the most cost-effective approach [Erstad, 2004]. This picture may continue to evolve if oral or low-dose IV PPI can be shown to be as efficacious as high-dose IV PPI in preventing adverse outcomes. As the cost of IV PPI decreases with the expiration of its patency and the introduction of generic formulations both in oral and IV forms, it is likely that the cost differences between oral and IV PPI will become less significant. The main clinical impact will be seen in a decrease in the length of hospitalization associated with giving oral PPI postendoscopic hemostasis, or even avoiding hospitalization altogether in selected patients who can be managed in an outpatient setting. Risk stratification tools such as the Blatchford [Stanley *et al.* 2009; Blatchford *et al.* 2000], Baylor rebleeding [Saeed *et al.* 1995] and the Rockall scores [Rockall *et al.* 1996] may be valuable in determining the risk of adverse outcomes in patients with UGIH, and in turn help the decision making process of which form, and what dosage of PPI to use.

With regard to giving IV PPI pre-endoscopically, an analysis modeled on the results of the Lau *et al.* study concluded that the preemptive use of infusional IV PPI is cost-effective, as it reduces the cost of the endoscopic procedure and the length of hospitalization [Tsoi *et al.* 2008]. The drug-related costs are offset by the overall savings in the management of UGIH. The same conclusion was reached in a similar study in a Canadian setting [Enns *et al.* 2003], where the administration of pre-emptive IV PPI is already common practice. The overall savings will be made even more significant as the cost of IV PPI comes down with the introduction of its generic forms.

Intravenous PPI in the prevention of stress-related mucosal injury

Stress, defined as a response to the severe demands on the human body resulting in a disruption of homeostasis through physiological and psychological stimuli [Ali and Harty, 2009], has long been recognized to cause gastric mucosal damage. The pathophysiology remains poorly understood, and is thought to include the disruption of normal mucosal barrier defences due to hypoperfusion, ischemia and reperfusion, resultant oxidative stress, and gastric microcirculatory disturbances [Ali and Harty, 2009]. The prevalence of gastric lesions in critically ill patients is estimated to be 75% to 100% in the first 1–3 days of illness [Peura and Johnson, 1985; Czaja *et al.* 1974]. It is estimated that up to 25% of patients in critical care will develop clinically overt bleeding [Mutlu *et al.* 2001], defined as hematemesis, melena, gross blood or 'coffee grounds' in the nasogastric tube. Clinically significant bleeding, defined as bleeding associated with hemodynamic instability or a drop in hemoglobin requiring transfusion, occurs in 3–4% of patients only [Mutlu *et al.* 2001].

The strongest risk factors associated with stress-induced ulcer bleeding are respiratory failure (odds ratio [OR] 15.6) and coagulopathy (OR 4.3) [Cook *et al.* 1994]. Amongst patients with one or both of these risk factors, 3.7% developed clinically important bleeding. This was associated with a mortality rate of 48.5%, compared to 9.1% in patients without gastrointestinal bleeding ($p < 0.001$). Other less significant risk factors include hypotension, sepsis, acute liver failure, chronic renal failure, prolonged nasogastric tube placement and alcoholism [Ellison *et al.* 1996; Cook et al. 1994].

IV H2RA has long been established as efficacious prophylaxis for stress induced mucosal injury in critically ill patients [Cook *et al.* 1998; Cook *et al.* 1991], and is the most widely used drug for this purpose [Quenot *et al.* 2009]. Continuous IV H2RA is superior to intermittent bolus administration in maintaining intragastric pH at >4 [Siepler *et al.* 1989; Ostro *et al.* 1985]. IV PPI is probably superior to IV H2RA because of its greater potency and lack of tolerance problems, but there is little evidence to support this in the critical care setting, apart from a few small trials with heterogeneous variables [Quenot *et al.* 2009]. A recent multicenter, randomized trial assessed the effects of intermittent IV pantoprazole on intragastric pH in 200 patients in intensive care. The administration of various doses of IV pantoprazole (40 mg every 12 or 24 h, and 80 mg every 8, 12 or 24 h) was compared with continuously infused cimetidine (30 mg bolus followed by 50 mg/h). The study found that, on any day, 80 mg of IV pantoprazole given every 8 h or 12 h achieved the greatest percent time where the intragastric pH was >4, but this was matched by 40 mg every 12 h on day 2 of the study [Somberg *et al.* 2008]. This suggests that an initial 80 mg every 8 or 12 h for the first 24 h, followed by 40 mg every 12 h from the second day onwards, may obtain the best acid suppressing results. However, it is not clear if high-level acid suppression is truly required, and the benefits must be weighed against the possible complications and side effects of administering IV PPI.

Box 4. Summary of IV PPI use in stress induced ulcer prophylaxis.

- Prophylaxis for stress-induced ulcers should be reserved for patients with high risk factors; for example, respiratory failure and coagulopathy.
- IV H2RA is commonly used although bolus IV PPI is probably as efficacious.

IV, intravenous; H2RAs, H2-receptor antagonists; PPIs, proton-pump inhibitors

Intravenous PPI in gastroesophageal reflux disease

It is well established that PPI therapy is one of the most effective therapies available for healing erosive esophagitis [Richter and Bochenek, 2000; Dekkers *et al.* 1999] Although it is uncommon for this condition to cause death, when severe enough, it is associated with significant morbidity such as bleeding ulcers, strictures and malignancy. It can also occasionally cause a patient significant dysphagia and odynophagia. IV PPI therapy in these settings may be useful.

With regard to the potency in suppressing gastric acid, there appears to be little difference between oral and IV PPIs [Keating and Figgitt, 2004; Kovacs *et al.* 2004; Metz *et al.* 2000]. The decision to administer IV bolus PPI probably rests on a patient's ability to swallow oral PPIs. In a pilot study looking at the safety and efficacy of high-dose infusional pantoprazole in the treatment of erosive esophagitis, patients with grade 4 esophagitis were randomized to receiving either high dose infusional or intermittent bolus IV pantoprazole (40 mg daily for 72 h) [Cai *et al.* 2008]. Both groups were treated with oral pantoprazole 40 mg daily for 4 days afterwards. Endoscopy on day 6 to 8 showed complete or significant healing of the esophagitis in the high dose infusional group, and partial or nil improvement in patients in the oral PPI group. The difference was statistically significant ($p = 0.015$), suggesting that high-dose infusional PPI is the fastest way to heal severe esophagitis, and that this is achievable in a matter of days. However, none of the patients in either group experienced any complications during the study. Whether this strategy is cost-effective, and in what scenario this will be most clinically meaningful, requires further study.

Box 5. Summary of IV PPI use in gastroesophageal reflux disease.

- IV and oral PPI appear to be equally efficacious in suppressing gastric acid.
- IV PPI is useful in patients who have severe erosive esophagitis and are unable to tolerate oral therapy.
- Infusional IV PPI can heal erosive esophagitis in a matter of days. Its clinical benefit over IV bolus PPI remains unknown.

IV, intravenous; PPIs, proton-pump inhibitors.

Intravenous PPI in the treatment of Zollinger-Ellison syndrome

A gastrinoma is a rare but important neuroendocrine tumor which generally originates in the proximal duodenum or pancreas. It can occur sporadically or in association with the multiple endocrine neoplasia (MEN)-1 syndrome. ZES is characterized by the uncontrolled secretion of gastrin by the tumor, resulting in the hypersecretion of gastric acid, profuse diarrhea, and severe and refractory peptic ulcer disease. Its incidence is estimated to be 0.1 to 3 per million in the US.

Potent gastric acid suppression is paramount in the treatment algorithm of ZES, as complications arising from the hypersecretion of gastric acid and severe ulceration are responsible for significant morbidity and mortality. The ideal goal is to reduce the basal gastric acid output to <10 mEq/h for uncomplicated ZES, and <5 mEq/h for complicated ZES, such as that occurring in association with MEN-1, GERD, or after gastrectomy [Maton, 1996].

Historically, high dose H2RA has been shown to be effective in suppressing gastric acid secretion in ZES [Maton, 1996; Vinayek *et al.* 1993]. This has largely been replaced by PPI because of its greater potency and lack of development of tachyphylaxis. Oral PPI is safe and effective in maintaining the control of basal gastric acid output in ZES [Metz *et al.* 2003]. IV PPI may play a role when patients are unable to tolerate oral PPI, such as when they have severe bleeding ulceration, pre-operatively, or during chemotherapy if they have metastatic disease. A bolus of 80 mg IV pantoprazole has been shown to be effective in acid control (defined as <10 mEq/h) within 15–60 min of administration [Lew *et al.* 2000]. IV doses of 160 mg to 240 mg daily achieved 24-h acid control for 6 days, without any significant side effects. Patients entered this study in a hypersecretory state as the study required withholding the use of oral PPI for 7 days. In real-life practices, patients are usually on a degree of acid suppression already from oral PPI therapy. A multicenter study subsequently reported successful transition of oral PPI therapy (omeprazole 20–200 mg daily or lansoprazole 30–210 mg daily) to IV pantoprazole, without breakthrough gastric acid hypersecretion [Metz *et al.* 2001]; 93% of patients in this study achieved adequate acid control for 7 days (defined as <10 mEq/h or <5 mEq/h in patients with prior gastric reducing surgery) with 80 mg IV pantoprazole twice a day. One patient required a dose escalation to IV 120 mg twice a day.

Box 6. Summary of IV PPI use intravenous ZES.

- IV PPI may be useful in the pre-operative period or in patients who are unable to tolerate oral therapy. Switching from oral to IV PPI is safe.
- The majority of patients require IV 160 mg daily (80 mg b.d.). Some may require IV 240 mg daily.

IV, intravenous; PPIs, proton-pump inhibitors.

Adverse events associated with intravenous PPI

There remains a concern that acid-suppression increases the incidence of nosocomial pneumonia in ventilator-dependent patients. A meta-analysis has found that ranitidine is associated with increased odds of nosocomial pneumonia compared with sucralfate, which does not alter the intragastric pH [Messori *et al.* 2000]. In a large cohort study, the use of acid-suppressive drugs was associated with 30% increased odds for developing hospital-acquired pneumonia [Herzig *et al.* 2009]. The use of pantoprazole in critically ill patients has been shown to be an independent risk factor for nosocomial pneumonia (OR 2.7; 95% CI, 1.1–6.7, $p = 0.034$) [Miano *et al.* 2009].

The use of IV PPI is also common in cirrhotic patients, especially in those with acute UGIH, where the source of bleeding is often unclear initially. PPIs are also often used to prevent post-variceal banding ulcer formation. A recent study found PPI use to be an independent risk factor for the development of SBP in cirrhotics (OR 4.31; CI 1.34–11.7) [Bajaj *et al.* 2009]. One hypothesis for this association is that PPIs increase gut bacterial colonization, which can possibly lead to small bowel bacterial overgrowth [Thorens *et al.* 1996]. Bacterial translocation across the intestinal wall into the peritoneal cavity is thought to play a role in the pathogenesis of SBP. Of more concern though, is the fact that 47% of the patients receiving PPI in this study had no documented indication for PPI treatment [Bajaj *et al.* 2009].

Appropriate use of intravenous PPI

There is increasing concern that IV PPI is being prescribed inappropriately in the hospital and community setting. The use of IV PPI as prophylaxis against stress-related mucosal injury needs to be judicious. Routine prophylaxis is not cost-effective, and may subject patients to unnecessary side effects. It should be reserved for patients who are at higher risk of developing stress related ulcers. Acid-suppressive therapy is often inappropriately continued post ICU discharge, and even beyond hospital discharge in the community [Wohlt *et al.* 2007; Gardner *et al.* 2006]. Physicians should review and discontinue the use of IV PPI when the risk factors responsible for stress related mucosal injury are no longer present, and ensure that there is adequate

communication with the treating team upon a patient's transfer out of ICU, and also with the community medical care provider upon hospital discharge.

A prospective study of two American community-based teaching hospitals reported no acceptable indication in 56% of patients who received IV PPI during their hospitalization [Guda *et al.* 2004]. Of the patients who were started on PPIs for the first time, 81% were discharged with oral PPI upon discharge. Another study looking at the use of IV PPI in UGIH and non-UGIH patients has found that only 50% of UGIH patients received IV PPI for an appropriate indication, and that only 33% of non-UGIH patients were truly nil by mouth [Kaplan *et al.* 2005]. After implementing multidisciplinary intervention, including physician education, computerized dose template, pharmacists altering IV PPI orders in patients who were not nil by mouth, and recommending a GI consult when a PPI infusion is required, there was a significant absolute reduction in the degree of inappropriate prescription in the UGIH (26%; 95% CI 10–42%; $p < 0.0001$) and in the non-UGIH (41%; 95% CI 24–58%; $p < 0.0001$) subgroups. Increasing age and a low mean daily dose were found to be predictors of inappropriate use, with a trend seen for prescriptions written during evening shifts [Afif *et al.* 2007].

Box 7. Summary of IV PPI and adverse events.

- IV PPI has been associated with the development of nosocomial pneumonia in critically ill patients.
- PPI has also been linked to the development of SBP in cirrhotics.
- IV PPI in these patients should be used judiciously, and their indications frequently reviewed, as PPI is therapy is often inappropriately continued.

IV, intravenous; PPIs, proton-pump inhibitors; SBP, spontaneous bacterial peritonitis

Future directions

PPIs are widely used in practice, but several aspects of its use require further clarification. The clinical relevance of maintaining an intragastric pH of >6 in preventing rebleeding in peptic ulcers remains unclear. The efficacy and safety of high dose infusional IV PPI appears unarguable; convincing evidence will be required before the possibility of using low dose PPI can be realized. This debate between the use of high dose infusional, bolus IV and oral PPI, and their respective cost-effectiveness will likely be the focus of future studies in bleeding peptic ulcers. The possible synergistic effects of buffering agents in combination with PPIs may also be worth exploring. Using IV PPI appropriately will continue to be an issue in healthcare resource management.

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Conflict of interest statement

Dr Pang declares that there is no conflict of interest. In the last 2 years, Dr Graham has received small amounts of grant support and/or free drugs or urea breath tests from Meretek and BioHit for investigator initiated and completely investigator controlled research. Dr Graham is a consultant for Novartis in relation to vaccine development for treatment or prevention of *H. pylori* infection. He has received no payments in the last 2 years. Dr Graham is a also a paid consultant for Otsuka Pharmaceuticals and until July 2007 was a member of the Board of Directors of Meretek, Diagnostics, the manufacturer of the ^{13}C-urea breath test. Meretek was absorbed into Otsuka America in 2007. Dr Graham has received royalties on the Baylor College of Medicine patent covering materials related to ^{13}C-urea breath test. The patent will expire in October 2009 and no more royalties will be received after that time.

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