Potential Uses of Intravenous Proton Pump Inhibitors to Control Gastric Acid Secretion

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Key Words

Histamine H₂-receptor antagonists · Pantoprazole · Ulcer prophylaxis · Gastroesophageal reflux disease · Gastrointestinal bleeding · Intravenous administration

Abstract

Proton pump inhibitors are the most effective agents for suppressing gastric acidity and are the preferred therapy for many acid-related conditions. While proton pump inhibitors have been accessible in intravenous formulations in several European countries, they have been available only as oral drugs in the United States. In the near future, the proton pump inhibitor pantoprazole is likely to become available in an intravenous formulation for American patients. Potential uses for intravenous proton pump inhibitors include treatment of Zollinger-Ellison syndrome and peptic ulcers complicated by bleeding or gastric outlet obstruction, as well as prevention of stress ulcers and acid-induced lung injury. These intravenous proton pump inhibitors are also likely to be beneficial to patients undergoing long-term maintenance with oral proton pump inhibitors who cannot take oral therapy for a period of time. Intravenous pantoprazole is especially distinguished in its lack of clinically

relevant drug interactions, and it requires no dosage adjustment for patients with renal insufficiency or with mild to moderate hepatic dysfunction. Both omeprazole and pantoprazole are well tolerated in both oral and intravenous forms. Although further studies are needed to define their roles clearly, the availability of intravenous formulations of proton pump inhibitors will certainly assist with the treatment of gastric acid-related disorders.

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Introduction

Proton pump inhibitors (PPIs) are the most effective agents for suppressing gastric acid output. These agents have replaced histamine H₂-receptor antagonists (H₂RAs) for most standard indications, including the acute treatment of gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD), maintenance therapy for GERD or hypersecretory states, and prevention of ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs). Intravenous (IV) PPIs are not yet available in the United States, so continuous infusion or intermittent bolus H₂RAs remain the primary therapeutic modality in hos-

pitalized patients who cannot take oral medications. IV PPIs have been available in Europe for some time, and a number of uses for them have emerged. There are also limited US data supporting the use of IV PPIs for hypersecretory conditions. In the United States, IV pantoprazole may soon become available for use in hypersecretory conditions and for patients with idiopathic GERD who cannot take oral medications. Other potential indications for IV PPI therapy exist as well. This article first addresses conditions requiring inpatient antiseecretory therapy and then discusses current approaches with IV histamine H₂-RAs or oral PPIs. Finally, potential applications for IV pantoprazole in the acute care setting are presented.

Conditions Requiring Inpatient Antisecretory Therapy

Gastroesophageal Reflux

For the most part, IV PPIs will be used in hospital settings. Indications for antiseecretory therapy in hospitalized patients are likely to differ somewhat from indications in outpatient care (table 1). Because of the high prevalence of GERD in the general population, it is not uncommon for a hospitalized patient to have GERD as a concomitant condition [1]. While many hospitalized patients are able to continue their outpatient oral antiseecretory therapy, GERD treatment must be modified for some. Hospitalized patients who develop an acute exacerbation of GERD, or are unable to use enteral therapy due to an underlying medical condition, may require a change to IV therapy (table 1). Hospitalization itself may predispose a patient to the development of GERD. Endoscopic studies demonstrate esophagitis in as many as one third of patients in intensive care [2]. Risk factors for developing GERD symptoms during an acute hospital stay include prolonged bed rest and use of NSAIDs [1]. Thus, GERD therapy in some patients may need to be initiated in the hospital, often in an NPO (nil per os, or nothing by mouth) setting.

Bleeding Ulcers

A major risk factor for bleeding ulcers is the use of NSAIDs, especially in conjunction with corticosteroids [3]. Significant risk factors for rebleeding and/or mortality include massive initial bleeding, larger ulcers, an ulcer base with active hemorrhage or stigmata of recent hemorrhage, age of more than 60 years, and comorbid disease [3, 4]. Although most patients with PUD do not hypersecrete acid, acid clearly contributes to the development of

Table 1. Indications for oral and IV antiseecretory therapy

Oral therapy: traditional use in chronic acid-peptic conditions
GERD
Hypersecretory states
Prophylaxis for NSAID users
Prophylaxis for patients with prior PUD bleeding
Intravenous administration in hospitalized patients
Acute crises in patients with GERD, PUD or hypersecretory states
Complicated ulcer disease (bleeding and gastric outlet obstruction)
Stress ulceration prophylaxis
Perioperative aspiration prophylaxis

gastrointestinal (GI) ulcers. Peptic ulcers, including those due to *Helicobacter pylori* infection, NSAIDs, or hypersecretory conditions can heal in the presence of sufficient gastric acid suppression. Since platelet function and plasma coagulation are both pH-sensitive and since pepsin lyses clot at low pH, the maintenance of pH close to neutrality may influence bleeding rates [5]. Blood clots appear to be more stable at a pH above >6.0, and ongoing studies are examining whether gastric acid suppression may be useful in stopping ulcer bleeding and preventing rebleeding [6–8]. Patients with bleeding peptic ulcers who are initially managed in intensive care unit (ICU) settings are often kept NPO in case emergency surgery should become necessary. This necessitates parenteral inhibition of acid output in many patients before they resume an oral diet. Patients with PUD complicated by gastric outlet obstruction require either surgical bypass or prolonged IV antiseecretory therapy for healing and relief of the obstruction [6–8].

Stress Ulcer Prophylaxis

Agents that suppress gastric acid are frequently used in critically ill patients to prevent the development of stress ulcers. Endoscopic evidence of GI damage is common among critically ill patients, with an incidence approaching 100% for patients with severe trauma [9]. Up to 20% of these patients who do not receive prophylactic therapy manifest overt GI bleeding. Most studies indicate that such bleeding is associated with increased mortality [9, 10]. Established risk factors for stress ulceration in hospitalized patients are listed in table 2. The pathogenesis of stress ulcers is still not completely understood but, based on the available data, it appears that a gastric pH <4.0 increases the risk of stress ulceration [11, 12]. Although it

Table 2. Risk factors for stress ulcer bleeding [data from 13, 30]

Coagulopathy	Multiple organ failure
Head injury	Neurosurgery
Hepatic failure	Polytrauma
Hypotension, shock	Renal failure
Major trauma	Sepsis
Major surgery	Severe burns
Mechanical ventilation	Tetraplegia

has been demonstrated that neurosurgical patients and those suffering from head trauma experience hyperacidity, it has also been shown that many other critically ill patients have a high gastric pH [13]. Regardless of the underlying cause, parenteral acid suppression may reduce the risk of stress ulceration. Parenteral therapy should be used together with endoscopic management in hospitalized patients who bleed from stress ulceration.

Aspiration Pneumonia Prophylaxis

Acid-suppressing agents are also used in the perioperative setting to reduce the risk of lung injury from aspiration of gastric contents. Acid-induced lung injury is associated with a high mortality – approximately 40–50% [14]. Studies suggest that aspirated gastric acid causes lung injury via two mechanisms: direct injury and acid-induced activation of neutrophils. Neutrophils are the primary mediators of lung injury following aspiration of gastric contents [14, 15]. Although risk factors for acid aspiration continue to be debated, the literature suggests that patients with a gastric pH of <2.5 and a gastric volume of at least 25 ml are at greatest risk [16].

Intravenous Histamine Receptor Antagonists

Intravenous H₂RAs have been the mainstay of gastric acid control in the acute care setting. These drugs increase gastric pH through competitive inhibition of histamine H₂ receptors, and are effective in the treatment of various gastric acid-related conditions, including GERD, peptic ulcers, and Zollinger-Ellison syndrome (ZES). However, several factors limit the use of IV H₂RAs in the acute care patient. Histamine H₂RAs may be administered multiple times each day, but gastric pH levels fluctuate with bolus dosing. Continuous infusion smoothes out the peaks and troughs and is therefore preferred [17]. Continuous infusion may be logistically difficult in some patients, particu-

larly in those critically ill with limited IV access and who may already be receiving multiple IV medications. Slow gastric ulcer healing early in treatment [18] and the immediate development of tolerance also significantly limit the use of H₂RAs [19–21].

Bleeding Ulcers

Although H₂RAs are frequently used in the treatment of patients with acute upper GI hemorrhage, the data regarding their use for this indication are limited and conflicting. Supporting their empiric use is a meta-analysis of 27 randomized controlled trials in which more than 2,500 patients with acute upper GI hemorrhage used H₂RAs. This study of the literature pointed towards overall trends of reduced rebleeding, mortality and surgery rates of 10, 20 and 30%, respectively, with results statistically significant for the mortality and surgery groups only (p = 0.02 and 0.05, respectively). However, this meta-analysis is limited by the small size of the individual trials and in part by the high proportions of patients with successful outcomes in some studies. Furthermore, the benefits may be limited to those patients with bleeding gastric ulcers [22]. More recently, British investigators completed the largest multicenter randomized study in which patients with bleeding duodenal or gastric ulcers (n = 1,005) received famotidine or placebo. They found that famotidine did not have a significant effect on rebleeding, frequency of surgical procedures for bleeding, or mortality [5]. These results led them to argue against the routine use of H₂RAs to staunch GI bleeding. Despite the careful design of the British investigation, use of H₂RAs to control GI bleeding probably will continue but will remain controversial until additional prospective trials confirm the results of the British group.

Stress Ulcer Prophylaxis

Many critically ill patients receive IV H₂RAs for stress ulcer prophylaxis. Multiple studies have demonstrated that, compared with untreated controls or placebo, H₂RAs significantly reduce the frequency of both overt and clinically important GI bleeding [23]. Yet, some patients do not maintain a gastric pH >4.0, even with high-dose H₂RA therapy [12, 13, 24, 25], and many develop stress ulcers despite prophylaxis with these antagonists [26–28]. One randomized clinical trial documented a 20% incidence of overt GI bleeding in trauma patients receiving ranitidine, sucralfate or antacids [29]. Furthermore, some evidence indicates that H₂RAs may not influence mortality from stress ulcers [23]. A possible concern is evidence reporting that H₂RAs may promote bac-

Table 3. Potential uses of IV PPIs

Potential application	Supporting studies	Ref.
Reduction of gastric acid in patients with bleeding ulcers	Brunner, 1996	6
	Lin, 1998	44
	Baak, 1990	45
	Lanas, 1995	46
	Lind, 1986	47
	Brunner, 1992	51
	Brunner, 1990	52
	Hasselgren, 1997	88
Reduction of gastric acid in patients with ZES	Daneshmend, 1992	89
	Vinayek, 1991	54
	Maton, 1996	37
	Metz, 1998	53
Treatment of patients maintained over the long term with oral PPIs and who can no longer tolerate oral medications	Metz, 1999	68
	Paul, 1999	56
	Wurzer, 1998	57
Prevention of rebound hypersecretion	Fumagalli, 1998	58
	Plein, 1997	59
Prevention of risk of perioperative aspiration pneumonia	Bell, 1993	90
Reduction of the risk of perioperative aspiration pneumonia	Nishina, 1996	62
	Stuart, 1996	16
	Rocke, 1994	63
	Tripathi, 1995	64
Treatment of gastric outlet obstruction	Brunner, 1992	51
Prevention of stress ulcers	Yet to come	

terial overgrowth and put patients at increased risk for aspiration pneumonia [30, 31]. In a study of stress ulcer prophylaxis regimens, 13% of patients who developed nosocomial pneumonia had gram-negative retrograde colonization from stomach to trachea. This evidence supports the role of retrograde colonization as a possible etiology for nosocomial pneumonia in a small proportion of patients [29].

Use of Oral PPIs in Hospital Settings

It is well recognized that PPIs, such as omeprazole, lansoprazole and pantoprazole, are the most effective drugs available for suppressing gastric acid output. Multiple studies have proven PPIs to be more effective than H₂RAs in producing and maintaining symptom resolution and healing of esophagitis [32–35]. It is also well established that PPIs provide rapid symptom resolution and healing of duodenal and gastric ulcers. Furthermore, PPIs are accepted as the preferred treatment for NSAID-

induced ulcers and hypersecretory conditions such as ZES [32, 36, 37].

Although limited European data have suggested that IV PPI therapy is useful in hospitalized fasting patients, no IV formulations have been available in the United States. Physicians have been forced to improvise for patients unable to take oral medications. Several studies have investigated the efficacy of improvised PPI delivery methods in preventing stress ulcer development and/or elevating intragastric pH levels. One method involved breaking the capsule and crushing the granules to form a suspension of omeprazole which was subsequently administered via nasogastric tube [28, 38]. In a variant of this approach, the integrity of the unencapsulated enteric-coated granules was preserved in order to maintain the delayed-release activity of omeprazole [39]. In a third study, investigators administered intact lansoprazole granules together with orange juice through a gastrostomy tube [40]. Positive effects on intragastric pH levels were reported in these trials, but the lack of better controlled supporting studies and the use of drug delivery methods not approved by the Food and Drug Administration (FDA) for those compounds temper the significance and utility of these findings. It would be preferable to have a commercially available IV PPI preparation that could be given easily to patients unable to swallow whole capsules.

Potential Uses for IV PPIs

In the near future, an IV formulation of pantoprazole will likely become available in the United States, providing physicians with a counterpart to the IV PPIs already approved in Europe [41]. Approval from the FDA will initially be for use in hypersecretory conditions such as ZES and in GERD patients who cannot take oral medication. This IV PPI will undoubtedly be studied in a variety of potential additional settings and conditions, especially in the ICU and the operating room (table 3).

In studies with oral formulations, all four members of the PPI family, omeprazole, lansoprazole, rabeprazole and pantoprazole, have been found to be of comparable efficacy in treatment of acid-related diseases such as GERD [42, 43]. Similarly, IV formulations of pantoprazole and omeprazole have proved equally effective in treating upper GI bleeding [6]. These findings are not surprising, given that all PPIs act through the same mechanism, inhibition of the parietal cell H⁺K⁺-ATPase [43].

Control of Intra gastric pH

Intravenous PPIs may improve the management of patients with conditions in which rapid reduction of gastric acid output is desirable. For example, they may help in the management of patients with bleeding ulcers by fostering acid-base conditions that allow for more rapid clot organization and stabilization. Using either IV agent, pH levels >6.0 may be rapidly achieved and maintained with an IV bolus dose of a PPI followed by continuous infusion [6–8, 44]. The continuous infusion appears necessary to inhibit newly generated proton pumps and thereby maintain a nearly neutral gastric milieu [6–8]. The results of several studies suggest that IV PPIs provide better control of intra gastric pH than do H₂RAs [45–47]. A study of 100 patients randomized to omeprazole or ranitidine demonstrated that mean intra gastric pH rose to 6.0 an hour after the initial bolus and persisted close to that value for the rest of the 24-hour study period. In contrast, patients taking cimetidine collectively showed a mean intra gastric pH of 4.0 1 h after the initial bolus, and pH levels hovered around 4.5–5.5 for the remainder of the 24-hour period. The duration in time of the raised intra gastric pH (6.0) was $84.4 \pm 22.9\%$ (mean $\pm$ SD) in the omeprazole group, compared with $53.5 \pm 32.3\%$ in the cimetidine group ($p < 0.001$). A second study, a prospective, randomized, open clinical trial of 51 patients, found that the percentage of time that the gastric pH was <6.0 (in proteolytic range for pepsin) was $15.3 \pm 5.9\%$ for omeprazole (80-mg bolus and 40 mg/12 h IV) versus $61.8 \pm 5.6\%$ ($p < 0.0001$) in those treated with ranitidine (50 mg/4 h IV). Among current therapies, PPIs achieve the best gastric acid suppression.

Control of Gastric Ulcer Bleeding

Several studies suggest that, because of the rapid and nearly complete suppression of gastric acid seen with IV administration of omeprazole or pantoprazole, these drugs may prevent rebleeding in patients in whom peptic ulcer bleeding is initially controlled with endoscopic therapy [48–50]. The largest and most comprehensive of these investigations was a double-blind, multicenter study of 333 patients over the age of 60 with bleeding stigmata at initial endoscopy [49]. Patients were randomized to receive either omeprazole or placebo and were evaluated at 3 and 21 days. Day 3 results for omeprazole demonstrated statistical significance relative to placebo regarding duration ($p = 0.0032$), maximal severity of bleeding ($p = 0.012$), and overall outcome of treatment ($p = 0.017$). Results at day 21 confirmed a reduction in the need for surgery ($p = 0.02$) and blood transfusions ($p = 0.049$). Sim-

ilar results were discovered at the conclusion of a randomized, double-blind, multicenter study of 274 patients with endoscopically confirmed ulcer hemorrhage and a history or signs of circulatory failure, bleeding, or a visible vessel [48]. Statistically significant treatment success associated with omeprazole was defined by reductions in mortality, surgical procedures and endoscopic treatments ($p = 0.004$). Significant differences in favor of omeprazole were also found for secondary variables such as number of blood transfusions ($p = 0.01$), duration ($p = 0.02$) and severity of bleeding ($p = 0.03$). It should be noted that acid suppression should be accompanied by prevention of bleeding, shock prevention, and early endoscopic and surgical intervention when necessary.

Greater prevention of peptic ulcer rebleeding has also been documented with PPIs relative to H₂RAs [44, 50–52]. One study that compared omeprazole with ranitidine showed that bleeding stopped in 16 out of 19 (84%) patients using a continuous infusion of IV omeprazole, and only 3 out of 20 (15%) such patients given a continuous infusion of ranitidine for the same 5-day period ($p < 0.01$) [52]. A multicenter, open, parallel-group comparison of 133 patients with endoscopic hemostasis of peptic ulcer bleeding compared pantoprazole 40 mg and IV ranitidine for efficacy [50]. The study demonstrated a tendency for a lower rebleeding rate (confirmed by endoscopy at 48 h) in the pantoprazole group compared to the ranitidine group. However, the differences did not reach statistical significance. Rebleeding rates were 10% in both groups; mortality rates 1.5% in both groups. Taken together, these studies suggest that in comparison with placebo, use of a PPI in patients with endoscopically treated bleeding peptic ulcer produces statistically significant beneficial effects, reducing the number of operations and endoscopic treatments. Nonetheless, the significance of the potential benefits warrants further study for clarification. The relative efficacy of IV PPIs may prove superior to IV H₂RAs, but the pilot study reviewed above was limited by a small number of patients, lack of endpoints (only rebleeding rate), and a short duration (only 48 h). Further study will be needed.

Zollinger-Ellison Syndrome

The rapid onset of action of IV PPIs is likely to make these agents useful in the treatment of patients with ZES. Intravenous PPIs provide a means for controlling gastric acidity in ZES patients undergoing long-term maintenance therapy, who are temporarily unable to tolerate oral medication. Studies have demonstrated that IV pantoprazole rapidly controls gastric acid output in ZES patients

(within 1 h) [53]. Twice-daily administration of 80 mg IV pantoprazole effectively maintains control of acid output in most ZES patients previously treated with oral PPIs [53]. Studies with IV omeprazole have also demonstrated effective control of gastric acid output in ZES patients [37, 54].

Patients Unable to Take Oral Medication

In all probability, IV PPIs will also be used in a variety of patients undergoing long-term oral maintenance PPI therapy who can no longer tolerate oral medications (table 3). One study demonstrated that when patients previously maintained with oral pantoprazole for the treatment of GERD were switched to IV pantoprazole, efficacy was maintained [55]. Another study found consistent, uninterrupted relief of gastric distress [56]. Studies have also shown the efficacy of IV pantoprazole followed by oral pantoprazole in the initial treatment of reflux esophagitis. The efficacy of the IV and oral regimen was similar to that of an exclusively oral regimen [57–59].

Aspiration Pneumonia Prophylaxis

The preoperative administration of histamine H₂RAs decreases the risk of complications from aspiration following surgery [60, 61]. Intravenous PPIs have also shown promise when used in this setting. The rapid onset of acid inhibition by IV PPIs may be beneficial in patients undergoing emergency endotracheal intubation for cesarean delivery or major abdominal surgery. In one placebo-controlled study, preoperative administration of either oral omeprazole or lansoprazole significantly decreased gastric pH, gastric volume, and the risk of aspiration pneumonitis at induction of anesthesia [62]. Other studies have shown omeprazole to be superior to placebo [63] and superior to ranitidine in at least some parameters [16, 64].

Gastric Outlet Obstruction

In one clinical study limited by small sample size, IV omeprazole proved effective in resolving gastric outlet obstruction due to pyloric or duodenal ulcer. In 7 of 9 (78%) patients with pyloric ulcer and 3 of 5 (60%) patients with duodenal ulcer, 4-week treatment with 40 mg IV omeprazole 3 times daily healed the ulcers and cleared the gastric obstruction [51].

Stress Ulcer Prophylaxis

In the future, IV PPIs may also be used to prevent stress ulcers, particularly in patients with hyperacidity, such as neurosurgical patients or those suffering from

head trauma. Because of the possible association between a high gastric pH and the development of pulmonary infections, it is prudent that future studies examining the use of IV PPIs for stress ulcer prophylaxis also carefully assess the incidence of pulmonary infections. The ultimate role of IV PPIs in stress ulcer prophylaxis will depend upon the availability of data demonstrating unequivocal effectiveness in contrast to histamine H₂RAs and sucralfate [12, 65, 66].

Dosing Considerations

The majority of investigations on dosing of IV PPIs have been done with omeprazole and pantoprazole, and were generally short-term studies. A few reports have dealt with chronic conditions such as GERD, however, and, at least for pantoprazole, have concluded that oral and IV formulations are equivalent on a milligram-for-milligram basis. For example, a clinical trial that investigated the effectiveness of IV pantoprazole in healing moderate to severe erosive esophagitis and providing symptom relief to GERD patients found equivalence between the efficacy of oral pantoprazole for 8 weeks and IV pantoprazole for 5 days followed by oral pantoprazole for the remainder of an 8-week period [58]. Similar results have been found in a study that included 24-hour monitoring of intragastric pH in healthy volunteers, which demonstrated that the oral and IV formulations of pantoprazole at 40 mg/day are equipotent [67].

Dosing for ZES

Evidence confirms that higher and more frequent doses of IV PPIs are necessary to control the severe gastric acid hypersecretion that afflicts patients with ZES [53, 54, 68, 69]. Using IV omeprazole, twice-daily doses of 60 mg sufficed to control acid output in most ZES patients; for more refractory cases, 100 mg every 12 h proved sufficient [69]. Similarly, two recent clinical studies found that 80 mg of IV pantoprazole administered twice daily in 15-min infusions effectively controlled acid output (defined as acid output <10 mEq/h) for 7 days in the majority (70–93%) of ZES patients. A total daily dose of 240 mg was sufficient to stabilize acid output in patients who did not respond to the initial dosage [53, 68].

Dosing for Bleeding Ulcers

Acid secretion may also be higher in patients with bleeding ulcers compared with those with nonbleeding ulcers [70]. Consequently, more aggressive IV PPI thera-

py may be required to reduce acid output and elevate the intragastric pH to levels that permit healing. A dose-finding study indicated that 80 mg of IV omeprazole or IV pantoprazole administered over 2 min followed by a continuous infusion of 8 mg/h was optimal for treating patients with acute GI bleeding [6, 51, 71]. This dosing regimen increased intragastric pH to a level >6 within 20 min and maintained that level for 84% of a 24-hour period [6]. Similar IV PPI dosing regimens have been effective in the treatment of patients with duodenal, gastric and bleeding peptic ulcers [6, 72]; in one trial, the initial 80-mg bolus of IV omeprazole was followed by 40 mg twice daily, leading to cessation of bleeding in 84% of patients [52].

Dosing for Stress Ulcer Prophylaxis

Although the utility of IV PPIs in the prophylaxis of stress ulcers has been demonstrated in animal studies [73, 74], no clinical trials have yet been reported. Liquified suspensions of omeprazole, 40 mg/day, administered via nasogastric tube, have been tested in several studies with success [38, 39, 75]. Those studies as well as others involving IV H₂RAs have demonstrated that raising intragastric pH levels >4.0 in critically ill patients – a target readily achievable with IV PPIs [6] – can help prevent stress ulcer formation [76].

Safety of IV PPIs

The safety of oral PPIs is well established; the most common adverse events associated with these agents are diarrhea, nausea, skin disorders and headache [36]. Based on the data from studies with IV omeprazole and pantoprazole, it appears that IV PPIs are also well tolerated [47, 77]. Reports from Germany of impaired vision and blindness associated with IV administration of omeprazole were originally of some concern [78]. However, a review of clinical trial data and epidemiologic studies with oral omeprazole did not confirm this association; it was likely

a result of confounding coincident conditions [79]. Studies in the United States of IV pantoprazole demonstrated no ophthalmic effects.

Few drug interactions involving omeprazole, lansoprazole or pantoprazole have been reported. Although in theory pantoprazole is less inhibitory toward the cytochrome P₄₅₀ enzyme than are omeprazole or lansoprazole, this property has not yet proven to translate into a clinical advantage [80]. In over a decade of use of omeprazole, no serious clinical problems for most applications have been linked to effects on these enzymes [81]. The interactions that have been identified are generally not expected based on the metabolism of PPIs [82].

Nevertheless, pantoprazole deserves consideration in the ICU setting for patients receiving multiple medications, based on its lack of interactions with the cytochrome P₄₅₀ system. In the high-risk patient, physicians may prefer not to entertain any additional risk of interaction. Furthermore, pantoprazole requires no dosage adjustment in the elderly [83], in patients with renal insufficiency or on dialysis [84, 85], or in patients with mild-to-moderate hepatic impairment [85, 86]. In this respect, pantoprazole is differentiated from other PPIs, as this degree of independence of dosage is not shared by either lansoprazole or omeprazole [42, 87]. This feature will likely facilitate use of pantoprazole in ICU patients who experience changes in renal or hepatic function.

In summary: Intravenous PPIs provide a welcome addition to the antisecretory armamentarium and will expand the clinical applications of antisecretory therapy. While there are many potential uses for IV PPIs, further studies are needed to clearly define their efficacy and safety for each of these potential indications.

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