Pharmacology of acid suppression in the hospital setting: Focus on proton pump inhibition

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The more potent and longer-lasting inhibition of gastric acid secretion provided by proton pump inhibitors (PPIs) as compared with histamine-2–receptor antagonists is caused in large part by differences in their mechanism of action. PPIs block histamine-2–, gastrin-, and cholinergic-mediated sources of acid production and inhibit gastric secretion at the final common pathway of the H^+/K^+ adenosine triphosphatase proton pump. In contrast, histamine-2–receptor antagonists cannot block receptor sites other than those mediated by histamine. It seems that the rapid loss of acid suppression activity by the histamine-2–receptor antagonists may be attributed to tolerance. Such tolerance has not occurred in patients receiving PPIs because these agents are irreversible inhibitors of the H^+/K^+ adenosine triphosphatase proton pump. For these reasons, patients who have acid-related disorders that require high levels of acid suppression do not respond well to intravenous histamine-2–receptor antagonists and would be excellent candidates for intravenous PPI therapy. Candidates for intravenous PPIs also include patients who cannot receive oral PPIs and those who may need the higher acid suppression therapy provided by the intravenous rather than the oral route. Clinical studies have demonstrated the efficacy of intravenous pantoprazole in maintaining adequate control of gastric acid output during the switch from oral to intravenous therapy in patients with severe gastroesophageal reflux disease or the Zollinger-Ellison syndrome. Intragastric administration of solutions prepared from oral PPIs has been used as an alternative to the intravenous route in critical care settings. However, decreased bioavailability may limit the value of intragastric delivery of PPIs because of the high frequency of gastric emptying problems in critically ill patients. (Crit Care Med 2002; 30[Suppl.]:S356–S361)

KEY WORDS: gastric acid secretion; acid suppression; drugs; mechanism of action; severe intravenous; nasogastric; proton pump inhibitors; histamine-2–receptor antagonists; severe gastroesophageal reflux disease; Zollinger-Ellison syndrome

Acid-suppressive drugs that have the ability to reduce gastric acid secretion are used for the prevention and treatment of stress-related mucosal disease and other acid-related disorders (1, 2). The clinical effectiveness of intravenous histamine-2–receptor antagonists (H_2RAs) and intravenous proton pump inhibitors (PPIs) in acid-related disorders, and the greater clinical effectiveness of the latter, can be explained by an examination of the process of acid secretion. Both daytime and nighttime gastric acid secretion contribute to acid-related disorders, although evidence is accumulating that nocturnal acid secretion is implicated more in upper gastrointestinal mucosal damage and in various related complications (3–5). This article will discuss aspects of the pharmacology of the PPIs, the benefits offered to critically ill patients by PPIs, and the first intravenous PPI formulation, intravenous pantoprazole. Pharmacologic actions of PPIs will be discussed that provide a rationale for the greater and longer-lasting elevation of intragastric pH achieved by intravenous PPIs as compared with intravenous H_2RAs. As an alternative to the oral route, PPIs have been administered through a nasogastric tube for faster delivery and to provide enhanced acid suppression. Disadvantages of this method of PPI delivery also will be addressed. There are a number of conditions that may require intravenous acid suppression, including severe gastroesophageal reflux disease and the Zollinger-Ellison syndrome (ZES). Data from clinical trials will illustrate the benefits of intravenous pantoprazole in such patients.

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PHYSIOLOGY OF NOCTURNAL SECRETION OF GASTRIC ACID

The secretion of acid occurs at a continuous basal level and increases after meals (1, 6). Figure 1 (6) shows the pathways used in gastric acid secretion. Basal acid release is stimulated by food. When a meal containing protein is consumed, amino acids are released, which stimulate the release of gastrin by G cells in the antrum. This, in turn, stimulates the enterochromaffin-like cells of the stomach to release histamine. A recently described pathway, regulated by pituitary adenylate cyclase-activating polypeptide that is neurally released, plays a major role in nocturnal histamine secretion (7, 8).

Parietal cells located in the body and the fundus of the stomach are involved in the production of gastric acid (1). In response to various stimuli, these cells secrete hydrogen ions (1, 2, 9). Enterochromaffin-like cells in close proximity to the parietal cells secrete histamine, which binds to specific receptors on the parietal cells (1, 10, 11). The dominant mechanism for the secretion of acid seems to be the release of histamine from enterochromaffin-like cells stimulated by gastrin (1, 11). Calcium also may play an important role in the secretion of gastric acid, stimulating the parietal cells to release acid or to act through the G cells to stimulate the release of gastrin (12–15).

PPIS

The most potent available inhibitors of gastric acid secretion, PPIs, have revolutionized the treatment of acid-related disorders such as gastroesophageal reflux, ZES, and idiopathic hypersecretion (16). Newer applications for PPIs currently being investigated include therapy for patients with bleeding ulcers and prophylaxis of stress-related mucosal disease (16). The first PPI in the United States, omeprazole, was introduced in 1989. A second PPI, lansoprazole, became available in 1994 (16). Numerous clinical trials conducted with both these agents found them to be effective in relieving acid-related symptoms and to be associated with minimal side effects and drug interactions (2, 16, 17). Pantoprazole is one of the newer PPIs available in the United States (18). This agent has been used widely in European countries and elsewhere, both as an oral drug and an intravenous formulation (16). Pantoprazole is the first intravenous PPI formulation approved for use in the United States (19).

PHARMACOLOGIC PROFILE OF PANTOPRAZOLE

The chemical structure of pantoprazole, like that of all PPIs, is based on a benzimidazole ring. Available in an enteric-coated tablet, pantoprazole is freely soluble in water. Pantoprazole, similar to other PPIs, is a prodrug that must be first activated in an acidic environment. After its administration, it diffuses into the gastric parietal cells through their basolateral membrane (2, 16). This weak base then binds tightly to the proton pump (which is the adenosine triphosphatase enzyme) and inhibits its ability to produce gastric acid (2). Metabolism of pantoprazole in the liver to inactive metabolites occurs through a dual pathway by using the enzymes of the cytochrome P-450 system and sulfate conjugation (20–22).

Pharmacokinetic and Pharmacodynamic Properties. This PPI has a high absolute bioavailability (77%) in addition to a high level of serum protein binding (nearly 98%) (18). Its elimination half-life is 1 hr, similar to that of most PPIs. Pantoprazole has a minimal interaction with the cytochrome P-450 system, no food effect, and no active metabolites. Its lack of apparent drug interactions (20–22) is particularly useful to critically ill patients, who typically take numerous medications. Like all the currently approved PPIs, pantoprazole is chemically activated within the body (Fig. 2) (2). It is accumulated rapidly in the acid environment of the luminal canaliculi of the parietal cell membrane (23). The activated drug binds covalently with cysteine residues in the transmembrane domains 5 and 6 on the alpha subunit of the adenosine triphosphatase molecule (1, 23). This process blocks the action of the proton pump. Because of the drug's irreversible binding, subsequent secretion of acid can occur only with the synthesis of new pump enzyme, a process that takes up to 48 hrs (1, 23). The relatively low pH of its activation (pKa = 3.96) compared with other PPIs offers the advantage of being activated only in the highly acidic canalicular space rather than in other tissue sites with a higher pH, such as the kidneys, brain, or intestines.

The reason that PPIs are more potent inhibitors of gastric acid secretion than H_2RAs may readily be understood by looking at a schematic representation of the parietal cell (Fig. 1) (6). Receptors for acetylcholine, histamine, and gastrin are present on the mucosal surface of the parietal cell (2, 24). Stimulation of one of these receptors initiates a series of reactions that results in acid secretion. Although H_2RAs effectively block the histamine receptor, the gastrin and acetylcholine receptors are not blocked, and activation of either can lead to the secretion of gastric acid. In contrast, PPIs inhibit the proton pump, the final step in acid secretion, and therefore block the effects of stimulation of all three receptors (2, 24).

INTRAGASTRIC OR INTRAVENOUS DELIVERY OF PPIs

Compared with H_2RAs, the greater ability of PPIs to maintain a higher gastric pH is related to the latter's irreversible binding to the proton pump, which renders this enzyme inactive. Moreover, the tachyphylaxis that is commonly associated with H_2RAs does not occur with PPIs (25). Until March 22, 2001, when the intravenous formulation of pantoprazole was approved by the U.S. Food and Drug Administration, only oral preparations of PPIs were available in the United States, administered as intact capsules or pills. An intragastric preparation was prepared by mixing the contents of the enteric-coated granules of omeprazole or lansoprazole with a sodium bicarbonate solution, orange juice, or even water and delivered by means of a nasogastric tube (26–30).

The nasogastric formulation also has been studied as prophylaxis for stress-related mucosal bleeding (31). Although a PPI administered in this fashion to critically ill patients at risk for such bleeding

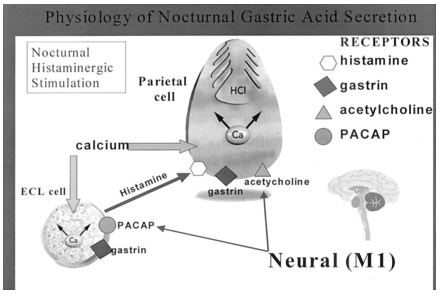

Figure 1. Physiology of nocturnal gastric acid secretion. How histamine-2–receptor antagonists and proton pump inhibitors suppress gastric acid secretion. *ECL*, enterochromaffin-like; *PACAP*, pituitary adenylate cyclase–activating polypeptide; *M*, muscarinic. Adapted with permission from Modlin and Sachs (6).

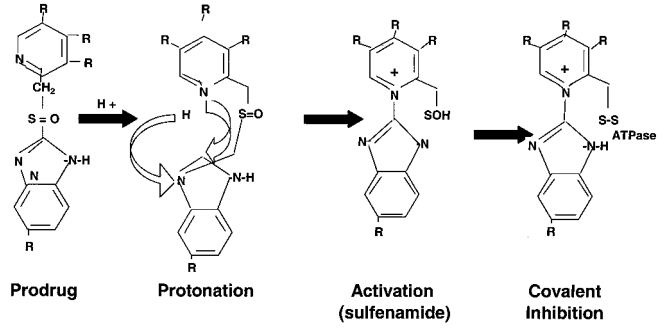

Figure 2. Binding of proton pump inhibitors to the H^+/K^+ adenosinetriphosphatase (*ATPase*) proton pump. This diagrammatic representation shows the activation of PPIs within the parietal cell secretory caniculus and covalent binding to this enzyme that is responsible for suppression of gastric acid production. Adapted with permission from Wolfe and Sachs (2).

seemed to decrease the rate of clinically important or significant bleeding and elevate intragastric pH (31, 32), a number of problems are associated with these findings. A major deficiency in these studies is use of a different definition of clinically important bleeding than that employed in the benchmark studies by Cook et al (33, 34). Moreover, the lack of pharmacokinetic data makes it unclear whether the reported increases in intragastric pH are caused by sodium bicarbonate or by the absorption and subsequent inhibition of acid secretion by PPIs. Absorption into the gastric lumen does not activate oral PPIs; oral doses must reach the systemic circulation before activation and acid suppressive action.

Other problems associated with nasogastric delivery of PPIs include decreased bioavailability, adherence to the plastic tube, and destruction of granules by gastric acid that can result in unpredictable pharmacokinetics and antisecretory effects (35, 36). A loss of up to 10% of granules occurs when omeprazole is placed in a water solution and delivered via a nasogastric tube (36). Granules also may clog small-bore feeding tubes. These problems do not occur when the omeprazole granules are mixed in sodium bicarbonate, which dissolves the protective enteric coating; the high pH of this solution seems to protect the drug from destruction by stomach acid (31). A significant problem with all nasogastric solutions is the frequency of gastric emptying abnormalities in critically ill patients, which may adversely affect bioavailability of oral PPIs (37). Moreover, preparation of the nasogastric solution is time consuming and difficult for nurses in an ICU setting. Intravenous formulations of PPIs would obviate concerns regarding bioavailability.

There are no trials comparing the clinical efficacy of intravenous vs. oral PPIs. Given the prevalence of gastric motility abnormalities and other bioavailability issues observed with orally administered agents, it would seem that the only way to ensure adequate control of gastric pH in critically ill patients is to use either intravenous formulations of H_2RAs or PPIs. The issue of oral vs. intravenous drug administration applies not only to stress ulcer prophylaxis, but to all other drug administration as well. When critically important medications are indicated, the intravenous route usually is preferable.

CONDITIONS THAT MAY REQUIRE INTRAVENOUS ACID SUPPRESSION

Oral formulations of PPIs have been extremely beneficial in the management of several acid peptic disorders. In a number of circumstances, intravenous forms of PPIs may be necessary. Patients who would benefit from an intravenous PPI or who may require a change from oral to intravenous administration include hospitalized individuals who cannot tolerate oral intake, persons with severe gastroesophageal reflux disease, those with ZES who undergo gastrinomal resection, and those with idiopathic hypersecretion (Table 1). Other situations in which intravenous acid suppression should be considered include prophylaxis of stress-related mucosal disease, the management of acute gastrointestinal bleeding, the prevention of rebleeding, and the induction of anesthesia (16, 38).

Severe Gastroesophageal Reflux Disease. A chronic disorder, gastroesophageal reflux disease affects nearly 40 million Americans. An array of symptoms commonly known as heartburn has a profound impact on the quality of life of a large number of individuals (16, 39). Many patients experience a relapse after responding to initial therapy and may require life-long therapy (40). The results of switching from oral to intravenous pantoprazole were evaluated in a randomized, double-blind, placebo-controlled trial that assessed the ability of intravenous pantoprazole to maintain control of acid output in 65 nonfasting patients with gastroesophageal reflux disease who had a history of erosive esophagitis (41). Basal acid output and pentagastrin-stimulated maximal acid output were compared in patients whose medication was switched from oral to intravenous pantoprazole. The primary efficacy end point was maximal acid output 22–24 hrs after the last oral dose and the maximal acid output after the last intravenous dose. As a secondary efficacy end point, mean basal acid output was examined 24 hrs after the last oral dose and after the first and last intravenous doses.

After a prescreening period, all 65 patients were randomly assigned to two treatment groups: either 20 mg or 40 mg of oral pantoprazole for 10 days. At the end of this oral phase of the study, patients in both groups were further randomly assigned to receive either an identical matching dose of intravenous pantoprazole or a placebo. The results indicated that patient symptoms were well controlled with either 20 or 40 mg of oral pantoprazole, with an maximal acid output at or below 14.5 mEq/hr (41). Seven days after patients were switched to the intravenous regimen, the maximal acid output of the patients who received placebo increased to approximately 30 mEq/hr. In contrast, acid output in patients who received intravenous pantoprazole was well controlled, at either 10 mEq/hr in the 20-mg group or 7 mEq/hr in the 40-mg group (Fig. 3) (41). In patients receiving the drug for 7 days, no serious adverse events were noted, and side effects that did occur generally were minimal and caused by the placement of the nasogastric tube or by a local reaction to the injection.

ZES. Although relatively rare, ZES is a well-known cause of hypersecretion of acid (1, 2). The majority of patients with this syndrome have sporadic ZES (42). These patients tend to be fairly young (in their 40s and 50s) and otherwise generally healthy, with no other concurrent medical problems. Patients with ZES have a tumor in the duodenum or pancreas that releases high levels of gastrin, generally in the range of 700 to 1500 pg/mL. Not only does gastrin stimulate changes in the stomach, such as hypertrophy and hyperplasia of the parietal cells, it also stimulates acid secretion, resulting either in severe reflux or peptic ulcer disease. The objective of gastric acid control for patients who have ZES is reduction of the basal acid output to <10

Table 1. Suggested indications of intravenous proton pump inhibitors (PPIs)

Conditions that may require intravenous acid suppression with a PPI
Patients with GERD requiring a switch from oral to intravenous dosing
Patients with ZES requiring a switch from oral to intravenous dosing
Acute GI bleeding
Prophylaxis of stress ulcers and clinically important bleeding
Prevention of rebleeding from peptic ulcer disease
Induction of anesthesia

GERD, gastroesophageal reflux disease; ZES, Zollinger-Ellison syndrome; GI, gastrointestinal.

mEq/hr in those who have intact stomachs and to <5 mEq/hr in patients who have had prior acid-reducing surgery (43, 44).

A multiple center trial was conducted to evaluate the ability of intravenous pantoprazole to control acid hypersecretion caused by ZES (44). Of the 21 study subjects, 13 were men and 8 were women; 14 had sporadic ZES and 7 had ZES associated with multiple endocrine neoplasia syndrome type I (MEN-1). Their mean age was 52. The study population had a mean basal acid output of 40.2 mEq/hr and a mean fasting serum gastrin level of 930 pg/mL. All patients discontinued PPI therapy (omeprazole or lansoprazole) for 7 days to produce a level of hypersecretion before the administration of intravenous pantoprazole. During this washout period, patients were given 750–1200 mg of oral ranitidine every 6 hrs to protect them from the effects of hypersecretion; this regimen was stopped 30 hrs before the first dose of intravenous pantoprazole (44). The initial dose of intravenous pantoprazole was 80 mg, administered twice daily as a bolus infusion over a period of 15 mins. If acid control was not achieved with lower doses, the total daily dose was raised to a maximum of 240 mg (divided into three equal doses). Pantoprazole was given for 6 days (44). To prevent patients from developing active ulcer disease, periods of gastric acid collection were added to the protocol before the next scheduled intravenous dose. This made it possible to modify the dose periodically if the acid output was not controlled.

The results showed that intravenous pantoprazole controlled gastric acid output in all patients. A dose of 80 mg every 12 hrs controlled acid output effectively in 81% of patients (17 of 21 patients) (Fig. 4) (44). The remaining four patients required higher doses, possibly because of a rapid metabolism; two patients required a regimen of 120 mg every 12 hrs, and the other two patients required 80 mg every 8 hrs. Pantoprazole provided rapid control of acid output, with 8 of 21 patients attaining control within 30 mins; the mean and median times for controlling acid in these patients each were <46 mins. Control of acid output was maintained up to 12 hrs after the last dose was administered. The mean acid output in all patients receiving pantoprazole was <2 mEq/hr, with a range of 0 to 7.4 mEq/hr, a level well below the threshold required to prevent acid peptic complications and to permit mucosal healing (44).

Once the safety and efficacy of intravenous pantoprazole had been established for patients with ZES who had been withdrawn from antisecretory therapy and were hypersecreting when the intravenous drug was administered (44), a study was undertaken to determine whether patients with ZES whose acid output was well controlled by an oral PPI could be switched to an intravenous PPI without any loss of efficacy. The mean acid output in patients receiving an oral PPI (omeprazole or lansoprazole) was compared with their acid output after switching to intravenous pantoprazole (45). The study subjects included nine men and five

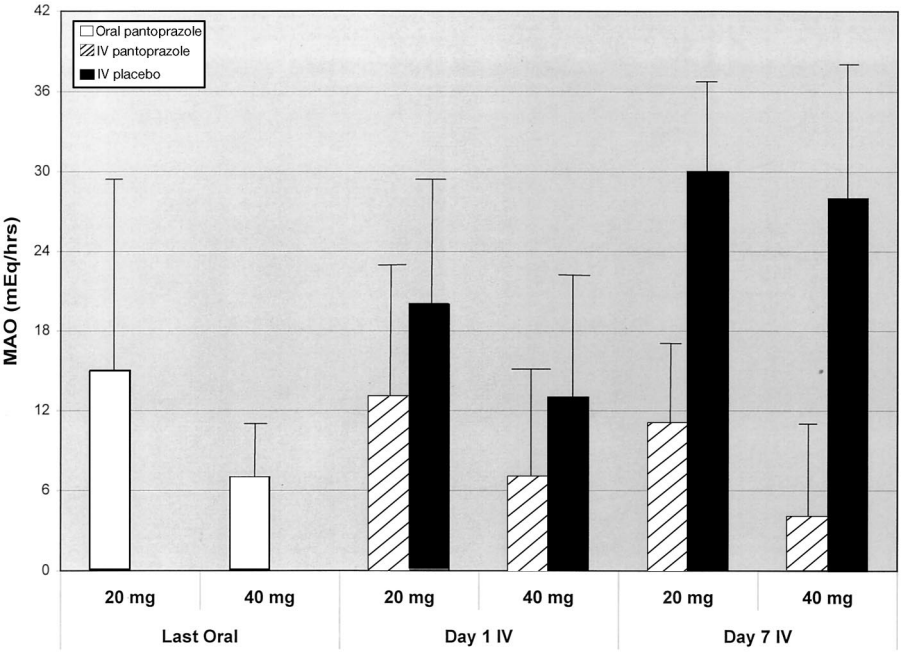

Figure 3. Maintenance of control of gastric acid output by intravenous (*IV*) pantoprazole in patients with severe gastroesophageal reflux disease during switch over from oral proton pump inhibitors. *MAO*, maximal acid output. Adapted with permission from Metz et al (41).

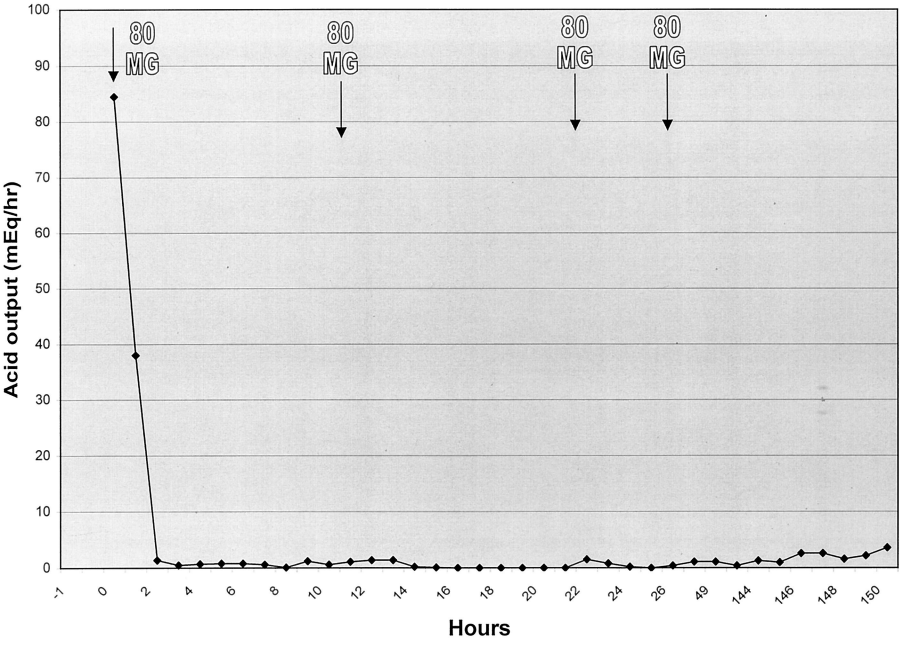

Figure 4. Control of acid output in patients with Zollinger-Ellison syndrome by intravenous pantoprazole. Note that acid output is rapidly inhibited and remains controlled, below 10 mEq/hr. Adapted with permission from Lew et al (44).

A comparison of proton pump inhibitors and histamine-2–receptor antagonists on the major sites of gastric acid production in the parietal cell clearly demonstrates why proton pump inhibitors are more effective when high levels of suppression of gastric acid production are required.

women, with a mean age of 52. Before oral PPI therapy, all subjects had been hypersecretory, with a mean basal acid output of 42 ± 35 mEq/hr, and hypergastrinemic, with a mean fasting serum gastrin of 1089 pg/mL.

In this trial, the primary efficacy end point for both the oral and intravenous drugs was a mean acid output below threshold. As discussed previously, acid output <10 mEq/hr is the desired threshold level in patients with ZES and intact stomachs; the level sought in those who have received acid-reducing surgery is <5 mEq/hr (43, 44). On days 1 through 4, acid output was measured for 1 hr before the first intravenous dose. On day 7, acid output was determined 11 hrs after the final intravenous PPI dose (45). The results indicate that a dose of 80 mg every 12 hrs maintained effective acid control during the switch in 13 of the 14 patients throughout the study period (45). The efficacy of oral and intravenous dosing were the same. The mean acid output in patients with ZES who received oral therapy and in 13 of the 14 patients switched to intravenous pantoprazole was <1.0 mEq/hr (Fig. 5) (45). No evidence of tachyphylaxis was seen with pantoprazole in these trials.

It has been generally believed that activation of the proton pump and subsequent secretion of gastric acid can occur only after a meal. As discussed earlier, PPIs can only be activated in the acid environment of the parietal cell and are

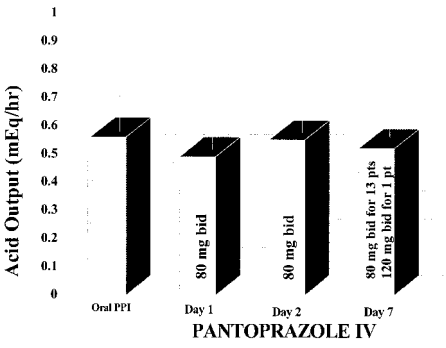

Figure 5. Maintenance of control of acid output in patients with Zollinger-Ellison syndrome who are switched from an oral proton pump inhibitor (*PPI*) to intravenous pantoprazole. Note the similar level of gastric acid output control. *bid*, twice a day. Adapted with permission from Metz et al (45).

ineffective in blocking gastric acid output in the absence of active proton pumps secreting acid (2). Therefore, it has been assumed that intravenous PPIs would be ineffective in patients who cannot receive enteral feeding. However, it seems that some pumps remain active and continuously secrete low levels of acid (46). This continuous output of acid may explain why administration of an intravenous PPI was effective in rapidly raising the intragastric pH to ≥4.0 and maintaining this pH for at least 2 days in 68 critically ill patients who could not receive enteral feeding (47).

CONCLUSION

A comparison of PPIs and H_2RAs on the major sites of gastric acid production in the parietal cell clearly demonstrates why PPIs are more effective when high levels of suppression of gastric acid production are required. This is relevant to patients with severe gastroesophageal reflux disease and to those with ZES or other acid hypersecretory conditions. PPIs administered intravenously offer a faster onset of gastric acid suppression than those given orally; they also maintain intragastric pH closer to neutrality and offer greater bioavailability in critically ill patients. PPIs retain their acid suppressing activity in patients who could not receive enteral feeding in an ICU setting. Preliminary data show that an intravenous PPI was able to rapidly raise intragastric pH to ≥4.0 and maintain this pH for at least 2 days in critically ill patients (46).

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Post-test answers: 1.d, 2.a, 3.a, 4.d, 5.d, 6.a, 7.b, 8.a, 9.a, 10.a