

by James M. Hoffman, PharmD

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Pantoprazole Sodium for Injection

(Protonix® I.V.-Wyeth Laboratories)

Summary

Indications: Intravenous pantoprazole is an alternative short-term treatment (7-10 days) for patients with gastroesophageal reflux disease (GERD) who cannot take pantoprazole tablets. It is not indicated for initial treatment of GERD. Intravenous pantoprazole is also indicated to treat pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome (ZES) or other neoplastic conditions.¹ Although not FDA-approved for the treatment of GI bleeding, intravenous pantoprazole has also been used to treat this condition.

Monitoring Parameters: The most common adverse events associated with intravenous pantoprazole include abdominal pain, chest pain, rash and pruritus.

Dose: The labeled dose of intravenous pantoprazole is 40 mg once daily for 7-10 days.

Pediatrics: Safety and effectiveness have not been determined in pediatric patients.

Geriatrics: The pharmacokinetic and safety profile of intravenous pantoprazole in geriatric patients is similar to younger patients.

Pregnancy: Category B. Reproductive studies in rats at four times the recommended human dose and in rabbits at six times the recommended human dose did not find impaired fertility or fetal harm.

Breast Feeding: It is not known if pantoprazole is excreted in human milk. However, pantoprazole and its metabolites are excreted in the milk of rats and caution should be exercised when using this drug in nursing women.

Stability and Reconstitution: Vials should be reconstituted with 10 mL of 0.9% sodium chloride, and further diluted with 100mL of 5% dextrose, 0.9% sodium chloride, or lactated Ringers. Vials may be stored at room temperature for up to two hours after reconstitution. Admixed solution may be stored at room temperature for up to twelve hours before administration.

Administration: Due to precipitates that form after admixture, intravenous pantoprazole must be administered through a dedicated line with the supplied filter. It should be administered over at least fifteen minutes.

Cost: Intravenous pantoprazole is supplied as a freeze-dried powder in 40mg vials. The average wholesale price per vial is \$24.00.

A Call for Contributions

For over 4 years, the University of Wisconsin Hospital and Clinics' Center for Drug Policy has been proud to contribute articles to *JPSW* on topics we hope have been of interest to pharmacists in a wide variety of practice settings. This month, James Hoffman provides an evaluation of a parenteral proton-pump inhibitor, IV pantoprazole, along with guidelines for its use. I believe this topic will be of significant interest to pharmacists practicing in the hospital setting, but may be of limited interest to our colleagues in community practice.

I would be very interested to hear from PSW members with ideas for future installments of *Pharmacotherapy Perspectives*. I would also be grateful to any member interested in contributing an article to this column. If you have a topic to suggest, or a manuscript you are interested in submitting, please contact me by phone at 608/262-7537 or via E-mail at lc.vermeulen@hosp.wisc.edu. Please help us continue to make this column and our journal an important resource for Wisconsin pharmacy.

—Lee Vermeulen, Column Editor

Introduction

Since the introduction of the first proton pump inhibitor (PPI) in 1989, PPIs have consistently been among the most commonly prescribed class of medications.² PPIs are highly effective for the treatment of various acid secretion disorders, including GERD and ZES. Although not FDA-approved for use in GI bleed, intravenous pantoprazole has generated interest for this indication.

Until the recent introduction of intravenous pantoprazole, only oral dosage forms of PPIs were available. Intravenous omeprazole is available in other countries but has not been introduced in the United States due to potential risk for ocular toxicity, including blindness.³ Although controversial, the risk of ocular damage with intravenous omeprazole is minimal.⁴⁻⁶ Lim-

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ited data are available for the use of intravenous pantoprazole. Because data are often extrapolated from studies that evaluate intravenous omeprazole, omeprazole studies are also reviewed in this monograph.

Pharmacology/pharmacokinetics

Pantoprazole inhibits gastric acid formation by binding to the H⁺K⁺-ATPase enzyme system in gastric parietal cells.¹ Since the H⁺K⁺-ATPase enzyme system is the final pathway for all acid secretion, acid secretion is inhibited regardless of its origin.

Intravenous pantoprazole has a terminal elimination half-life of one hour and displays linear kinetics.¹ Although the half-life of intravenous pantoprazole is short, acid suppression lasts for more than twenty-four hours due to binding to the H⁺K⁺-ATPase enzyme system. Pantoprazole is metabolized by the cytochrome P450 system in the liver and primarily eliminated in the urine. Dose adjustments are not required in renal or mild-moderate hepatic failure, but caution should be taken in patients with hepatic failure as the half-life may be prolonged.^{1,2} Pantoprazole is not removed by hemodialysis.

Clinical trials

Gastroesophageal Reflux Disease (GERD)

In a randomized study of twenty healthy subjects, equal doses of intravenous and oral pantoprazole produced equivalent levels of gastric acid inhibition.⁷ There was no significant difference between median pH after 24 hours (intravenous 3.3, oral 3.1). Similar results were found in a randomized, double blind study in sixty-five patients with GERD.⁸ Patients were randomized to receive 20 or 40 mg of oral pantoprazole for 10 days and then randomized again to receive intravenous pantoprazole or placebo for 7 days. Acid output was measured at the end of oral administration and after intravenous administration. No significant difference was found in basal or maximal acid output in either dose. After oral administration, acid output was 14.5 ± 15.5 mEq/hr in the 20 mg group and 6.5 ± 5.6 mEq/hr in the 40 mg group. After intravenous administration, acid output was 11.1 ± 10.2 mEq/hr in the 20 mg group and 6.6 ± 6.3 mEq/hr in the 40 mg group. In the placebo group, acid output was significantly different (29.2 ± 13.0 mEq/hr, p<0.05). Ophthalmic examinations were performed during the study and no ophthalmic adverse events were reported. Aside from rashes in three patients, no significant adverse events due to intravenous pantoprazole were observed in this study.

Zollinger-Ellison Syndrome (ZES)

Intravenous pantoprazole is indicated for the treatment of hypersecretion associated with ZES. Pentagastrin was administered to healthy volunteers to stimulate acid secretion as a model of ZES.⁹ The study was a dose-ranging study designed to determine the most effective dose of pantoprazole, onset of activity, and duration of acid suppression. Patients (n=39) received placebo, 20 mg of famotidine, or one of various doses of

intravenous pantoprazole (20, 40, 80, or 120 mg). Maximum acid output was measured at consistent intervals over a twenty-five hour period. Acid suppression took effect within 15 to 20 minutes. Although acid output was decreased at all doses for at least 16 hours, 80 or 120 mg of intravenous pantoprazole inhibited over 90% of acid secretion in all subjects for approximately 21 hours.

Patients with ZES were evaluated in a non-randomized study to determine the efficacy and safety of intravenous pantoprazole.¹⁰ Following a 7-day washout period, all twenty-one patients received 80 mg of intravenous pantoprazole every 12 hours. Doses were then increased to 120 mg every 12 hours or 80 mg every 8 hours depending on acid output. The maximum dose was 240 mg in 24 hours. Patients were treated for 3 to 6 days. The primary endpoint was acid output less than 10 mEq/hr. The majority of patients' (17 of 21, 81%) acid output was controlled with 80 mg every 12 hours. Two patients required 120 mg every 12 hours for acid control, and two required 80 mg every 8 hours. Once acid control was established, it was maintained for at least 24 hours. Despite the high doses employed in the study, few adverse effects were observed, and the most common adverse effect was headache. Ophthalmic examinations were performed during the study and no ophthalmic adverse events were reported.

Acute Gastrointestinal (GI) Bleed

The majority of acute GI bleeds develop in the upper gastrointestinal tract, and peptic ulcers are the most common cause of upper GI bleeds.¹¹ Most bleeds (80%) resolve spontaneously, but each year approximately 150,000 to 300,000 patients are admitted to United States hospitals for the treatment of an upper GI bleed. Annual mortality estimates range from 6 to 10% and have remained consistent over the last thirty years.¹² Standard management of acute GI bleed includes endoscopy and surgery when endoscopy is unsuccessful or unavailable. Meta-analysis has shown that endoscopy reduces mortality by 45% (odds ratio 0.55, 95% CI 0.40-0.76).¹³ In vitro, approximately neutral pH is necessary for optimal platelet aggregation and blood coagulation (Table 1).¹⁴ Although intravenous pantoprazole is not indicated for the treatment of acute GI bleeding, several small studies have evaluated its use in bleeding peptic ulcers. All available information on this application is in abstract form only at this time. There are no clinical trials published in their entirety that evaluated intravenous pantoprazole for the treatment of acute GI bleed.

In an open study without a control group, twenty patients with bleeding peptic ulcers received intravenous pantoprazole.¹⁵ Patients received a bolus dose of 80 mg of intravenous pantoprazole within 2 hours of hemostasis with endoscopy. The bolus dose was followed by a continuous infusion of pantoprazole at a rate of 8 mg/hr for 72 hours. Endoscopy was repeated after 72 hours. Patients then received 40 mg of intravenous pantoprazole every 12 hours for the next four days. The primary endpoint of the study was increase in

TABLE 1. PH VALUES AND COAGULATION STATUS

PH	Platelet/Coagulation Status
7.4	Platelet aggregation and coagulation is optimal
< 6.8	Platelet aggregation and coagulation is abnormal
< 6	Platelet disaggregation occurs; no platelet aggregation
< 4	Fibrin clots are dissolved

gastric pH. Two patients died due to rebleeding. The gastric pH of fourteen patients was available for evaluation. For the first 48 hours of therapy, the median pH remained above six 64.3% of the time and above four 97.5% of the time. The median pH for the entire period was 6.3. Thrombophlebitis occurred in four patients, but the authors state that a clear association was not observed. Because the endpoint was increase in gastric pH, no data on rates of rebleeding or surgery were reported.

The same investigators completed a similar study of twenty patients with bleeding peptic ulcers.¹⁶ Identical methods and endpoints were used except a continuous infusion of 6 mg/hr was used. The authors concluded that the 6 mg/hr infusion also effectively raised gastric pH, but that there was greater variability in response between individuals when compared to the 8 mg/hr dosing regimen in the study above. Specific details were not provided. Thrombophlebitis was not reported in this study.

Although these studies indicate that these regimens of intravenous pantoprazole may increase gastric pH, their small size and uncontrolled design do not allow one to draw any conclusion about the efficacy of intravenous pantoprazole for peptic ulcer bleeding.

In an open, randomized, multi-center trial a continuous infusion of intravenous pantoprazole was compared to a continuous infusion of ranitidine for the treatment of peptic ulcer bleeding.¹⁷ After endoscopic hemostasis, 66 patients were randomized to receive a bolus of 40 mg of intravenous pantoprazole followed by an infusion of 8 mg/hr for 2 days, and 67 patients received a bolus of 50 mg of ranitidine followed by an infusion of 12.5 mg/hr for 2 days. The two groups were comparable with regard to demographics, alcohol consumption, smoking, weight, height, body mass index, and Forrest stage of peptic ulcer bleeding. Patients were followed for up to ten days and no significant difference in mortality (1.5% in both groups) or rate of rebleeding (10% in both groups) was found.

Omeprazole for Acute Gastrointestinal (GI) Bleed

In a double blind, randomized, controlled trial performed in Hong Kong, 240 patients with bleeding peptic ulcers received 80 mg of intravenous omeprazole followed by an infusion of 8 mg/hr for 72 hours or placebo after endoscopic hemostasis.¹⁸ After the infusion, all patients received 20 mg of oral omeprazole for

8 weeks. Patients who tested positive for *H.Pylori* received treatment with omeprazole, clarithromycin, and amoxicillin. Only patients with ulcers that had a high risk of rebleeding (actively bleeding ulcers, ulcers with non-bleeding visible vessels, or clots with underlying vessels) were enrolled in the trial.

Placebo and treatment groups were comparable based on demographics, prevalence of other illnesses, severity of bleeding, risk factors for bleeding, and location of ulcers. Bleeding rates were significantly different between groups. Bleeding within 30 days occurred in 22.5% of patients in the placebo group, but in only 6.5% of the omeprazole group. Patients in the omeprazole group also required fewer units of blood (2.7 units vs. 3.5 units), and length of hospitalization was shorter (four days vs. five days). Intra-gastric pH was not recorded during the study. There was no difference in mortality between the two groups. Because Asians have a lower parietal cell mass than Caucasians, the generalizability to the U.S. population has been questioned.¹¹

Patients with bleeding peptic ulcers (n=100) were randomized to receive either intravenous omeprazole or cimetidine after hemostasis was achieved with endoscopy.¹⁹ Patients were enrolled in the study if they had active bleeding or non-bleeding visible vessels. The omeprazole group received a 40 mg bolus dose followed by an 8 mg/hr continuous infusion for three days. Intravenous therapy was followed by a daily dose of 20 mg of oral omeprazole for 2 months. The cimetidine group received a 300 mg bolus followed by a 50 mg/hr continuous infusion for 3 days. These patients received 400 mg of cimetidine twice daily for 2 months.

There were no significant differences between the demographic characteristics of the two groups. In this study, intra-gastric pH was recorded for the first 24 hours. Mean intra-gastric pH was approximately 6 in the omeprazole group and between 4.5 and 5.5 in the cimetidine group. The rate of rebleeding was significantly lower in the omeprazole group than the cimetidine group (2% vs. 24%; p=0.004). In addition, intra-gastric pH remained above 6 significantly longer in the omeprazole than the cimetidine group (84.4% of the time vs. 53.5% of the time, p<0.001). Patients in the omeprazole group required fewer blood transfusions, but the difference was not statistically significant. There was no difference in length of hospital stay, number of surgeries, or mortality rate. Since this study was also performed in an Asian population, the generalizability of this study might also be questionable.

A recent meta-analysis of nine trials that used omeprazole to treat bleeding peptic ulcers (all trials but one used intravenous omeprazole) showed that omeprazole decreased rebleeding and surgery but had no effect on mortality.¹⁴ The risk of rebleeding was reduced by 50% (OR 0.50, 95% CI 0.33 to 0.77; p=0.002), and the number needed to treat to benefit (NNTB) was 9 (95% CI 6 to 13). The need for surgery was reduced by 53% (OR 0.47, 95% CI 0.29 to 0.77; p=0.003), and the NNTB for surgery was

17 (95% CI 12 to 35). Mortality decreased by only 8% (OR 0.92, 95% CI 0.46 to 1.83, $p=0.81$).

Other trials

Lansoprazole administered nasogastrically in apple juice has been found to have similar effects on 24-hour gastric pH as intravenous pantoprazole.²⁰ Healthy volunteers ($n=33$) received either 30 mg of nasogastric lansoprazole or 40 mg of intravenous pantoprazole daily for five days. After a washout period, patients were crossed over to receive the other product. The lansoprazole group had a significantly higher pH than the intravenous pantoprazole group at both day 1 (3.05 vs. 2.76, $p<0.002$) and day 5 (3.65 vs. 3.45, $p=0.024$).

Adverse effects

In general, PPIs are well tolerated. The most common adverse effects observed with intravenous pantoprazole use include abdominal pain (12%), chest pain (6%), rash (6%) and pruritus (4%).¹ These adverse effects were not observed in the placebo group. Other less common adverse effects include headache, injection site reaction, dyspepsia, nausea, diarrhea, vomiting, dizziness and rhinitis.

Although reports of ocular toxicity prevented intravenous omeprazole from being marketed in the United States, there have not been reports of ocular damage with intravenous pantoprazole. Further study has shown this toxicity to be minimal. In a cohort study of 140,000 patients who received various anti-ulcer drugs (cimetidine, famotidine, nizatidine, omeprazole, ranitidine) the rates of ocular disorders were compared.⁶ The adjusted relative risk of vascular disorders of the eye for patients who received omeprazole was 1.8 (95% CI 0.5-6.0). The adjusted relative risk for vascular disorders of the eye for the entire cohort was 1.9 (95% CI 1.1-3.4). No cases of ocular disorders were reported in intravenous pantoprazole clinical trials.

Cost, dose, how supplied

Intravenous pantoprazole is supplied as a freeze-dried powder in 40-mg vials. The labeled dose of intravenous pantoprazole is 40 mg once daily for 7-10 days. The average wholesale price (AWP) is \$24.00 per 40 mg vial. In contrast, the AWP for a single pantoprazole 40 mg capsule is \$3.38.

For the treatment of an acute GI bleed (80 mg bolus followed by 8 mg/hr for 72 hours), the total drug cost of intravenous pantoprazole is \$393.60. In contrast, the lansoprazole regimen (60 mg every hour for 6 doses, 60 mg every 4 hours for 4 doses, then 60 mg twice daily) used at UWHC for acute GI bleeds would cost \$80.19.

Summary

Intravenous pantoprazole is the first intravenous PPI approved for use in the United States. It is effective for the treatment of GERD in patients who cannot take anything orally and ZES. Although studies have not been successful in raising intragastric pH to ideal levels, continuous infusions of high doses of intravenous pantoprazole may have some benefit for the treatment of acute GI bleeds. Evidence exists demonstrating that this strategy decreases the rate of rebleeding and surgery. Intravenous pantoprazole for the treatment of acute GI bleeds has not been shown to decrease mortality.

The drug is generally well tolerated, and the most common adverse effects are abdominal pain, chest pain, and rash. Special care must be taken when intravenous pantoprazole is administered. The drug must be given through a dedicated line with a filter.

Conclusion

Intravenous pantoprazole should not be routinely used in patients with GERD who are NPO. Intravenous ranitidine or nasogastric lansoprazole suspension should be used. Intravenous pantoprazole should not be used for stress ulcer prophylaxis. There are no published data that show intravenous pantoprazole is superior to other agents available for stress ulcer prophylaxis.

Considering the inadequate available data, the use of intravenous pantoprazole should be limited. An incremental benefit has been shown in patients with gastrointestinal bleeds who are at high risk for rebleeding. This would include bleeds prior to treatment with endoscopy and in bleeds characterized as spurting hemorrhage, oozing hemorrhage, non-bleeding visible vessel, or clot with underlying vessel. Intravenous pantoprazole is clearly beneficial for patients with ZES. The accompanying guideline outlines the UWHC approach to the use of intravenous pantoprazole. ■

References available on request.

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UWHC Guidelines for the Use of Intravenous Pantoprazole

(Protonix I.V.[®])

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A. Background

Since the introduction of the first proton pump inhibitor (PPIs) in 1989, PPIs have consistently been among the most commonly prescribed class of medications.¹ Intravenous pantoprazole was recently marketed, but there is limited available data on its use. In patients with certain types of bleeding peptic ulcers, PPIs have been shown to provide an incremental benefit for patients with bleeding peptic ulcers. PPIs decrease rebleeding episodes and may reduce the need for surgery.²⁻⁴ PPIs do not reduce mortality in patients with bleeding peptic ulcers, and endoscopy remains the primary treatment. Due to these factors, the use of intravenous pantoprazole must be limited to the uses outlined below.

B. Appropriate Indications for Use

1.0 Intravenous pantoprazole may be used to treat pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome (ZES) or other neoplastic conditions.⁵⁻⁶

2.0 Intravenous pantoprazole may be used to treat bleeding peptic ulcers before urgent endoscopy if there is evidence of significant bleeding.

3.0 After endoscopy the infusion should be stopped. Intravenous pantoprazole may continue to be used if the following criteria are met:³

3.1 Hemostasis has been achieved with endoscopy

AND

3.2 Endoscopy shows the ulcer is at high risk for rebleeding and can be categorized as one of the following:

3.2.1 Spurting hemorrhage

3.2.2 Oozing hemorrhage

3.2.3 Nonbleeding visible vessel

3.2.4 Clot with underlying vessel

C. Inappropriate Indications for Use

1.0 Intravenous pantoprazole may not be used simply because the patient is NPO. Intravenous ranitidine or nasogastric lansoprazole suspension should be used. Lansoprazole administered nasogastrically in apple juice has been found to have similar effects on gastric pH as intravenous pantoprazole.⁷ Intravenous pantoprazole does not provide better gastric pH control than oral pantoprazole.⁸

2.0 Intravenous pantoprazole should not be used for stress ulcer prophylaxis. There are no published data that shows intravenous pantoprazole is superior to other agents available for stress ulcer prophylaxis. Please refer to the drug guideline for stress ulcer prophylaxis for appropriate indications and medications for stress ulcer prophylaxis.

D. Contraindications

1.0 Intravenous pantoprazole is contraindicated in patients with known hypersensitivity to pantoprazole.

E. Dosing

1.0 In Zollinger-Ellison Syndrome (ZES) intravenous pantoprazole should be dosed as follows:⁶

1.1 Doses should be initiated at a dose of 80 mg every 12 hours.

1.2 The dose may then be titrated to a dose of 120 mg every 12 hours or 80 mg every 8 hours.

1.3 The maximum dose that should be used in ZES is 240 mg/day.

2.0 For bleeding peptic ulcers, intravenous pantoprazole should be dosed as follows:⁹

1.1 Patients should receive an 80 mg bolus after endoscopic hemostasis.

1.2 A 72-hour, 8 mg/hr continuous should begin immediately after the bolus dose.

1.3 After 72 hours, intravenous pantoprazole should be stopped (no benefit will be realized with longer infusions). Patients may be started on 40 mg of oral pantoprazole daily at this time.

F. Administration¹⁰

1.0 Due to precipitates that form after admixture, intravenous pantoprazole **must** be administered through a dedicated line with the supplied filter. Intravenous pantoprazole should not be administered with any other intravenous solutions.

2.0 In ZES, intravenous pantoprazole should be infused over 15 minutes.

3.0 In peptic ulcer bleeding, the bolus dose of intravenous pantoprazole should be given over 2 to 5 minutes.

4.0 Each bag of intravenous pantoprazole expires in twelve hours.

G. Pediatrics

1.0 Although safety and effectiveness have not been established in pediatrics, based on experience with omeprazole, a dose of 1mg/kg (without exceeding adult doses) of intravenous pantoprazole should be used. For further information, contact pediatric gastroenterology at 3-6420.¹¹

References available on request.