

Criteria for Use of Intravenous Pantoprazole

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

A summary of the literature review used to support the criteria for use of pantoprazole is available at <http://www.pbm.va.gov>.

Background

Pantoprazole is the first proton pump inhibitor (PPI) available in an intravenous formulation (pantoprazole for injection) in the U.S. It is FDA-approved for the short-term treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis and for pathological hypersecretion associated with Zollinger-Ellison syndrome.

Intravenous pantoprazole has also been used off label for short-term management of nonvariceal acute upper gastrointestinal bleeding (NVAUGIB). Most of the data supporting the use of PPIs for NVAUGIB have involved omeprazole, which is not available in an intravenous formulation in the U.S. For peptic ulcer bleeding (PUB), high-dose, continuous intravenous infusions of PPIs have been recommended, mainly based on pH studies rather than clinical outcomes. Until two years ago, a high-dose continuous infusion of omeprazole was also the only regimen evaluated and found to be efficacious for PUB in placebo-controlled trials in patients who had received endoscopic therapy. There is now evidence that high oral doses of PPIs may reduce re-bleeding rates after endoscopic hemostasis of PUB.

Although acid-suppressive agents are often used in the management of PUB, there is an insufficient number of well-designed trials to make definite conclusions about the role of PPIs either before or after endoscopic therapy. Their use should be tempered with the understanding that the potential benefits and risks of such treatment are uncertain.

VA Criteria for Use

1. Patient must be NPO

AND

2. ONE OF THE FOLLOWING CONDITIONS MUST BE MET:

Clinical signs of significant upper gastrointestinal bleeding before urgent endoscopy in patients with high risk for peptic ulcers

Confirmed active or recent peptic ulcer bleeding associated with endoscopic stigmata suggestive of high risk for re-bleeding (active acute hemorrhage, nonbleeding visible vessel (NBVV), or lesion with sentinel clot)

Bleeding or severe erosive esophagitis

Pathologic hypersecretion associated with Zollinger-Ellison syndrome

Contraindication to using histamine₂-receptor antagonists (H₂RAs) (e.g., H₂RA-related thrombocytopenia) for stress ulcer prophylaxis (SUP)

In studies that demonstrated efficacy of intravenous PPIs for high-risk PUB, the drug was administered *after* endoscopic diagnosis and hemostasis.^{1,2} There is a lack of clinical outcome evidence to support the use of intravenous PPIs in unselected patients with upper gastrointestinal bleeding. The recommendation that intravenous pantoprazole may be used for clinical signs of significant upper gastrointestinal bleeding *before* urgent endoscopy in patients with high risk for peptic ulcers is intended as temporary management in situations where endoscopy cannot be performed in a timely manner.

Inappropriate Indications for Use

- 1. Patient is not NPO.** In the absence of clinical outcome studies comparing oral with intravenous PPIs in PUB, these criteria recommend oral or nasogastric administration of PPIs for patients who are not NPO. Oral quadruple doses of omeprazole (80 mg per day in 2 or 4 divided doses) have been shown to reduce rates of re-bleeding following endoscopic hemostasis of PUB.^{3,4} In healthy volunteers, oral and intravenous doses of pantoprazole produce similar effects on intragastric pH,⁵ and nasogastric lansoprazole is at least as effective as intravenous pantoprazole in controlling intragastric pH.^{6,7} Once patients are no longer NPO, intravenous pantoprazole should be discontinued and PPI therapy continued orally or nasogastrically.
- 2. Stress ulcer prophylaxis.** There is limited published evidence to support the routine use of intravenous PPIs over H₂RAs for stress ulcer prophylaxis. Intravenously administered pantoprazole should not be used for SUP in the presence of thrombocytopenia that is not temporally or causally related to H₂RA use. Intravenously administered H₂RAs should be used in such cases.
- 3. Temporary conversion of an oral PPI in a patient who is made NPO, but who does not have an upper GI bleed or a contraindication to H₂RAs.** This includes temporary, short-term use in intensive care patients for uncomplicated gastroesophageal reflux disease or other indications unrelated to critical care illness. Intravenous H₂RAs should be used in these situations if continued acid-suppressive therapy is determined to be clinically appropriate.

Contraindications

Documented hypersensitivity to pantoprazole

Dosage

Peptic ulcer bleeding	40 mg i.v. bolus then 6.7 mg/h continuous infusion x 72 h (160 mg/d after bolus) OR 80 mg i.v. bolus then 8 mg/h continuous infusion x 72 h (192 mg/d after bolus)
Bleeding or severe erosive esophagitis	40 mg i.v. once daily for 7 to 10 days
Pathologic hypersecretion/Zollinger-Ellison syndrome	80 mg i.v. every 12 hours; may increase to 80 mg every 8 hours if needed; may titrate to higher doses depending on acid output
Stress ulcer prophylaxis	80 mg i.v. every 12 h for 24 h followed by 40 mg every 12 h

For PUB, high-dose continuous intravenous infusions of pantoprazole that provide a total of 160 mg per day after a 40-mg bolus⁸ or 192 mg per day after an 80-mg bolus^{1,2} may be used, as there is insufficient evidence and no consensus on the optimal dose. A quadruple-dose regimen of pantoprazole (160 mg i.v. per day in 2 or 4 divided doses) can be derived from results with orally administered omeprazole^{3,4}; however, these intravenous intermittent dosage regimens have not been studied in patients with PUB.

If PUB is not confirmed on urgent endoscopy, intravenous doses of pantoprazole should be discontinued. If PUB at high risk for re-bleeding is found on endoscopy, pantoprazole may be continued for 72 hours after hemostasis is achieved with endoscopic therapy. After 72 hours, the intravenous infusion of pantoprazole should be discontinued and oral PPI therapy at standard doses should be started.

If the patient must remain NPO after 72 hours, pantoprazole should be given as intermittent intravenous doses of 40 mg once daily until the patient can be converted to oral PPI therapy. Since intravenous and oral doses of pantoprazole have been shown to be equivalent in terms of pH control,⁵ this recommended intravenous dose of pantoprazole is the same as the off-label oral doses used for healing and maintenance of peptic ulcers.⁹⁻¹⁷

When intravenous pantoprazole is used for clinical signs of significant upper gastrointestinal bleeding before urgent endoscopy in patients with high risk for peptic ulcers, it should be continued for up to 72 hours or until endoscopy is performed. Therapy should then follow the recommendations above based on the endoscopic findings and patient's NPO status.

For oral administration, quadruple doses of a PPI (e.g., omeprazole 80 mg, rabeprazole 80 mg, or lansoprazole 120 mg daily, each given in 2 or 4 divided doses for 5 days), are suggested for PUB. For nasogastric administration for PUB, the same dose of omeprazole may be given as a Simplified Omeprazole Suspension^a or lansoprazole may be administered as a mixture of the enteric-coated granules in apple juice, or a Simplified Lansoprazole Suspension.^a

Dosing in Special Patient Populations

At standard doses, no dosage adjustment is necessary in elderly patients, patients with renal impairment, patients with hepatic impairment, or patients on hemodialysis. Higher than standard intravenous doses of pantoprazole have not been studied in these patient populations and therefore no recommendation can be made.

Administration

Intravenous boluses of pantoprazole should be given over 2 to 5 minutes.

Sodium chloride 0.9% solution is recommended for reconstituting and diluting pantoprazole for injection. Admixtures of pantoprazole for injection must be administered intravenously through a dedicated line, **using the in-line filter provided**. The filter removes precipitate that forms when the reconstituted drug is mixed with intravenous solutions and does not affect drug concentration. If a Y-site is used, then the in-line filter should be positioned below the Y-site that is closest to the patient. No other drugs should be concomitantly administered through the dedicated line.

The venous line should be flushed before and after administration of pantoprazole for injection with dextrose 5%, sodium chloride 0.9%, or lactated ringer's solution for injection. Pantoprazole for injection should not be simultaneously administered through the same line with other intravenous solutions.

Admixtures of pantoprazole for injection are stable at room temperature for 12 hours.

Table 1 shows the method that is being used to prepare pantoprazole infusions in the manufacturer's study investigating the use of pantoprazole for injection in the prevention of re-bleeding after endoscopic treatment of PUB (data on file, Wyeth Pharmaceuticals).

Table 1 Administration method for high-dose infusion of pantoprazole (80 mg + 8 mg/h)

Loading dose: 80 mg over 5 min
– Reconstitute 2 vials of pantoprazole (40 mg/vial) by injecting 10 ml of NS into each vial. This will provide a total of 80 mg per 20 ml.
– Remove and discard 35 ml from a 50-ml minibag of NS for injection. Inject the contents of the two reconstituted vials of pantoprazole (20 ml) to the solution remaining in the NS minibag (15 ml). This will result in a final concentration of 2.3 mg/ml in a final volume of 35 ml.
– In order to infuse the required loading dose of 80 mg over 5 minutes, infuse at the rate of 420 ml/h (7 ml/min = 35 ml/5 min).
Continuous infusion: 8 mg/h for 72 h
– Since admixtures should not be administered beyond 12 h from the time of admixture, bags were changed every 8 h.
– For each 8-h period, reconstitute 2 vials of pantoprazole (40 mg/vial) by injecting 10 ml of NS into each vial. This will provide a total of 80 mg per 20 ml.
– Add the 2 reconstituted vials of pantoprazole (20 ml) to a 400-ml bag of NS. This will provide a final concentration of 80 mg/520 ml (0.154 mg/ml). In order to infuse the required dose of 8 mg/h, infuse at a rate of 52 ml/h for 72 h.

Drug Costs

The intravenous doses of pantoprazole suggested by this guidance are 6 to 7 times more expensive than quadruple oral doses of rabeprazole or lansoprazole.

^aSimplified Omeprazole Suspension: 2 mg/ml 8.4% sodium bicarbonate; stable for 1 week at room temperature or 24 weeks frozen (non-oral syringe); protect from light. 18. Phillips JO, Metzler MH, Johnson M. The stability of simplified omeprazole suspension (SOS) (abstract). *Critical Care Medicine* 1998;28:A221. Simplified Lansoprazole Suspension (SLS): 3 mg/ml 8.4% sodium bicarbonate; stable for 14 days at room temperature or 28 days refrigerated (non-oral syringe).²⁹

Daily drug acquisition costs

Pantoprazole i.v.		Rabeprazole p.o.	Lansoprazole p.o.
6.7 mg/h (40-mg bolus)	8 mg/h (80-mg bolus)	80 mg/d	120 mg/d
\$15.28 (\$3.82)	\$18.34 (\$7.64)	\$2.60	\$2.60

FSS prices, April 2003. Prices for pantoprazole i.v. do not include intravenous minibags or infusion tubing.

Evidence Table

Strength of Recommendation and Evidence Rating	References	Quality of Evidence	Overall Quality
Grade A (always indicated and acceptable):			
No studies			
Grade B (may be useful/ effective):			
Quadruple-dose, orally administered PPI (omeprazole 20 mg every 6 h or 40 mg every 12 h) for prevention of re-bleeding of high-risk PUB after endoscopic hemostasis	Kaviani (2003) ³ Javid (2001) ⁴	I I	Good
High-dose intravenously administered PPI (omeprazole 80 mg then 8 mg/h or doses shown to maintain intragastric pH > 6.0) for prevention of re-bleeding or surgery in high-risk PUB after endoscopic hemostasis	Lau (2000) ¹ Sharma (2001) ²	I III (abstract)	Fair
Prefer high-dose, intravenously administered PPI (omeprazole 40-mg bolus then 6.7 mg/h infusion) over H ₂ RA for high-risk PUB with non-bleeding visible vessel	Lin (1998) ⁸	I	Fair
Prefer nasogastrically administered PPI (omeprazole) over H ₂ RAs for stress ulcer prophylaxis	Levy (1997) ¹⁹ Phillips (1998) ²⁰	I III (abstract)	Fair
Grade C (may be considered):			
Prefer intravenously administered pantoprazole (40 mg i.v. x 3 over 72 h) over H ₂ RAs for prevention of re-bleeding or surgery in high-risk PUB	Duvnjak (2001) ²¹ Fried (1999) ²²	III (abstract) III (abstract)	Poor
Intravenously administered H ₂ RAs for stress ulcer prophylaxis	Cook (1996) ²³ Messori (2000) ²⁴ Hanisch (1998) ²⁵ Metz (1993) ²⁶	I I I I	Good
Prefer intravenously administered PPI (pantoprazole) over H ₂ RAs for stress ulcer prophylaxis	Morris (2002) ²⁷	III (summary)	Poor
Grade D (may not be useful/ effective; possibly harmful):			
Prefer high-dose, intravenously administered PPI (omeprazole) over H ₂ RAs for active PUB (Forrest Ia or Ib, spurting or oozing)	Lin (1998) ⁸ Villanueva (1995) ²⁸	I I	Good
Grade I (insufficient evidence to recommend for or against):			
Optimal intravenous dosing regimen of PPI	Insufficient evidence	—	—

Evidence rating scheme based on the methods used by the third U.S. Preventive Services Task Force²⁹

Key to Quality of Evidence rating: I = At least one properly done randomized controlled trial; III = Opinion of respected authorities, case reports, expert committees

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