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Pharmacy & Therapeutics

Update

Drug Information for Health Care Professionals

May 2009

Evaluation of Intravenous Proton Pump Inhibitor Use: *Medication Use Evaluation*

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MUSC has established guidelines and a pre-printed clinician order form to encourage the appropriate use of intravenous (IV) pantoprazole in the adult population. The guidelines address appropriate and inappropriate indications for IV pantoprazole, doses, duration, eligibility for oral therapy, and alternative choices. While all inpatient services are required to use the pre-printed clinician order form, use of IV pantoprazole is not restricted to any particular service. Appropriate indications for use of IV pantoprazole at MUSC are listed in Table 1.

Evidence suggests that proton pump inhibitor (PPI) continuous infusions are more effective than intermittent infusions in reducing the rate of rebleeding in endoscopically treated patients with active non-variceal upper gastrointestinal bleeding (NVUGIB). The possibility exists that patients who require a continuous infusion are inappropriately receiving a PPI intermittent infusion. Additionally, patients are receiving IV PPI therapy without an appropriate indication.

FDA-approved indications for the use of IV pantoprazole include the following: gastroesophageal reflux disease (GERD) associated with erosive esophagitis (40 mg daily) or pathological gastric hypersecretion (80 mg every 8-12 hours).[1] Additionally, consensus recommendations for off-label use of IV pantoprazole for NVUGIB have previously been established.[2]

Table 1: Appropriate Indications for IV Pantoprazole Use

Definite or probable evidence of non-variceal upper gastrointestinal bleeding (NVUGIB)
Documented bleed and/or treatment failure while on histamine-2 receptor antagonist (H2RA) or sucralfate when oral therapy is not clinically feasible
Documented hypersecretory condition (e.g., Zollinger-Ellison syndrome or idiopathic) when oral therapy is not clinically feasible

It should be noted that IV PPIs are merely adjunctive therapy for high-risk patients (ie, those with endoscopic evidence of active bleeding, a visible vessel in an ulcer bed, or a clot in an ulcer bed) who have been treated endoscopically with hemostatic agents or for those patients who are awaiting endoscopy.[2] According to published guidelines, an endoscopy should be performed within 24 hours of suspicion of an active upper gastrointestinal bleed (GIB). An IV bolus followed by continuous infusion PPI is recommended for patients who have undergone successful endoscopic therapy for prevention of rebleeding.[2,3,4] The recommended dose for documented NVUGIB is an 80 mg bolus followed by 8 mg/h continuous infusion for 72 hours. Intravenous pantoprazole continuous infusions generally should not be continued beyond 72 hours since the risk of rebleeding after that time is low.

The use of IV PPIs for stress ulcer prophylaxis (SUP) is controversial.[5,6] Guidelines support the use of medications for SUP in the following patients: those who are mechanically ventilated for >48 hours and those with a coagulopathy, renal failure, or admitted to the intensive care unit (ICU) for thermal injury or spinal cord injury.[7,8,9] The Surviving Sepsis Campaign provides guidelines to support the use of histamine-2 receptor antagonists (H2RAs) over PPIs and sucralfate in all patients with severe sepsis.[10]

Currently, there is a lack of evidence to support the use of IV PPIs as first-line agents for SUP. The American Society of Health-System Pharmacists (ASHP) Commission on Therapeutics Guidelines for SUP from 1999 states that there is insufficient evidence to support that IV PPIs are superior to IV H2RAs for SUP.[8] Furthermore, there are a lack of comparative data with IV PPIs and IV H2RAs. While there is limited evidence to support the use of IV PPIs in SUP, some clinicians may prefer these agents based on their ability to maintain a gastric pH $\geq$ 4 for prolonged periods.[9,11,12,13] Edelman and colleagues endorse the following exceptions for the use of IV PPIs for SUP: thrombocytopenia associated with H2RAs, refractory gastric pH despite adequate H2RA therapy, or suspected or documented *Helicobacter pylori* infection.[11]

With the low incidence of stress ulcers and the lack of superiority of PPIs for this indication, it is reasonable to utilize the most cost effective therapy while considering each patient individually.[9,12,13] At MUSC, the use of IV PPIs for SUP is generally considered inappropriate.

Inappropriate indications for IV pantoprazole use include SUP, lower GIB, and GERD, unless the patient has had documented treatment failure with first-line agents (eg, oral pantoprazole, sucralfate, IV or oral famotidine). Oral therapy should be considered when patients have adequate oral intake by mouth or GI access device without diarrhea, vomiting, malnutrition or malabsorption.

Inappropriate use of IV PPIs at other institutions has been identified, and institutional guidelines and pre-printed order forms have shown mixed results with regard to improvement in use.[5,9,13-15] Proposed reasons for inappropriate use of IV pantoprazole at MUSC may include the following: lack of education about indications, doses, duration of therapy and alternatives; poor assessment of eligibility for oral therapy; delay in transition to oral therapy; failure to document past treatment failures; and variability in patient care. The primary objective of this medication use evaluation (MUE) was to evaluate the general appropriateness of IV pantoprazole use at MUSC. The secondary objectives were to determine reasons for inappropriate use of IV pantoprazole, evaluate the potential cost of inappropriate use, and provide recommendations for improvement.

METHODS

Institutional review board (IRB) approval was obtained for this MUE. Every order occurrence for IV pantoprazole in adult patients from March to October 2008 was included in the evaluation. Electronic reports were generated that included the following: patient demographics (eg, age, gender), ICU and hospital length of stay, IV pantoprazole dose, duration of therapy, enteral and parenteral nutrition orders, endoscopy reports, GI disease states, cost, and attending physicians. In addition, a retrospective chart review of the available patient information databases was conducted and the following data was collected: indications, eligibility for oral alterna-

tive medications, laboratory values, and other data as necessary for the purposes of the evaluation.

Use of the pre-printed clinician order form for IV pantoprazole was noted during data collection. If patients received IV pantoprazole for probable NVUGIB, lack of endoscopy within 24 hours was considered inappropriate use unless the patient exhibited the following: coffee ground nasogastric (NG) tube aspirate; guaiac-positive NG tube aspirate; guaiac-postive stools; hematemesis; hematochezia; melena; decrease in systolic blood pressure of more than 20 mmHg within 24 hours of bleed; increase in heart rate of more than 20 beats per minute within 24 hours of bleed; or decrease in hemoglobin of more than 2 g/dL within 24 hours of bleed.[4,16] For NVUGIB, the appropriate dose was considered 80 mg bolus followed by 8 mg/h continuous infusion for up to 72 hours. Use of the continuous infusion beyond 72 hours was considered inappropriate.

Doses and duration of therapy were collected for patients receiving IV pantoprazole intermittent infusions. Inappropriate use of intermittent IV infusion was determined largely by eligibility for oral therapy. Patients were deemed eligible for oral therapy if they received either 2 or more medications or enteral nutrition by mouth or a GI access device for at least 24 hours. For those patients receiving an intermittent infusion but not eligible for oral therapy, treatment failure with other acid-suppressive agents was determined. Treatment failure was defined as receiving an oral PPI as an outpatient or a trial of H2RAs or sucralfate prior to initiation of IV pantoprazole. In addition, evidence of thrombocytopenia (platelet count < 100,000), GERD with erosive esophagitis, *Helicobacter pylori* infection, and H2RA allergy were investigated. Any documented inappropriate indications for the use of IV pantoprazole outside of the pre-printed order form were noted, including SUP, lower GIB, and GERD. Descriptive statistics were performed on the data. Data are reported as median and interquartile ranges (IQR) because the patient population was not normally distributed.

RESULTS

Data were collected on 535 order occurrences of IV pantoprazole from March to October 2008 (Table 2). The median age of the patients was 55 years (range 18-97; IQR 45-66) and 51% were male. The median hospital length of stay was 6 days (range 0-185; IQR 3-16), and the median ICU length of stay was 1 day (range 0-85; IQR 0-5.5). The pre-printed clinician order form was not used in 22% (n = 117) of order occurrences.

Thirty-one percent (31%) of orders (n = 165) were continuous infusions and 69% (n = 370) were intermittent infusions. Of those who received continuous infusion, 50% (n = 83) had an endoscopy performed within 24 hours. Of those who received continuous infusion and did not have an endoscopy within 24 hours (n = 82), 44% (n = 36) had evidence of NVUGIB. The median duration of the continuous infusion was 3 days (range 1-16; IQR 2-4).

Of those who received intermittent therapy, 59% (n = 218) were eligible for oral therapy. The most frequent intermittent doses were 40 mg IV every 12 hours

Table 2: Use of IV Pantoprazole

Continuous Infusion 31% (n = 165)	
Median infusion duration: 3 days (range 1-16; IQR 2-4)	
Endoscopy performed within 24 hours	50% (n = 83)
Endoscopy not performed within 24 hours	50% (n = 82)
Had evidence of NVUGIB	44% (n = 36)
Intermittent Infusion 69% (n = 370)	
40 mg IV every 12 hours	67% (n = 249)
Eligible for oral therapy	**60% (n = 150)**
Median therapy duration: 4 days (range 1-32; IQR 2-5)	
40 mg IV every 24 hours	27% (n = 99)
Eligible for oral therapy	**58% (n = 57)**
Median therapy duration: 3 days (range 1-17; IQR 2-6)	
TOTAL eligible for oral therapy	**59% (n = 218)**
TOTAL ineligible for oral therapy	41% (n = 152)
On PPI at home OR failed H2RA or sucralfate trial	71% (n = 108)
Had thrombocytopenia	30% (n = 46)
Had GERD with erosive esophagitis	3% (n = 5)
Tested positive for *Helicobacter pylori*	3% (n = 4)
Had H2RA allergy	1% (n = 2)

(67%, n = 249) and 40 mg IV, every 24 hours (27%, n = 99). Of those who received 40 mg IV, every 12 hours, who were eligible for oral therapy (58%, n = 150), the median duration of therapy was 4 days (range 1-32; IQR 2-5). Of those who received 40 mg IV, every 24 hours, who were eligible for oral therapy (n = 57), median duration of therapy was 3 days (range 1-17; IQR 2-6). Of those who received intermittent therapy and were not eligible for oral therapy (41%, n = 152), 71% (n = 108) failed previous treatment with first-line therapies, 30% (n = 46) had thrombocytopenia, 3% (n = 5) had GERD with erosive esophagitis, 3% (n = 4) tested *Helicobacter pylori* positive and 1% (n = 2) had an H2RA allergy.

Specific documentation of inappropriate indications was noted in 20% (n=106) of order occurrences. Providers listed the following inappropriate indications for IV pantoprazole: 9.5% (n=51) SUP, 2.8% (n=15) GERD, 2.1% (n=11) lower GIB, and 5.4% (n=29) other. Furthermore, all intermittent infusion occurrences in patients eligible for oral therapy were also considered inappropriate. As stated above, of those who received intermittent therapy, 59% (n=218) were eligible for oral therapy; therefore, 59% of intermittent occurrences were deemed inappropriate.

Inappropriate use of IV pantoprazole has financial impacts on both the organization and the patient. The estimated cost and savings of an IV to oral conversion of inappropriate pantoprazole use are detailed in Table 3. Therefore, preventing inappropriate IV pantoprazole intermittent infusion use at MUSC will provide cost savings to the institution and prevent patients from incurring unnecessary expenses during their hospital stay.

Table 3: Costs of Inappropriate Use of IV Pantoprazole

Medication	Dosage	Cost Per Unit ($)		Schedule	Median Days of Inappropriate Use (n)	Cost Per Course of Therapy ($)		Patients Eligible for Oral Therapy (n)	Total Costs ($)	
		Hospital	Patient			Hospital	Patient		Hospital	Patient
Pantoprazole	40 mg	5	99	Q12 hr	4	40.32	792	150	6048	118,800
				Q24 hr	3	15.12	297	57	862	16,929
Total	-----	-----	-----	-----	-----	**55.44**	**1089**	-----	**6910**	**135,729**

CONCLUSIONS

By restricting use of IV pantoprazole to the order form, providers are exposed to appropriate and inappropriate indications, doses and duration of therapy, as well as alternative choices. The prescribing of continuous infusion pantoprazole was largely appropriate, so further intervention regarding its use is not necessary. However, the inappropriate use of intermittent infusions, predominantly 40 mg IV every 12 hours or every 24 hours, is an area where further intervention may be beneficial. Despite a mandatory order form, inappropriate use primarily involved either noncompliance of the form or inadequate review and understanding of the information on the form. Providers may be more likely to overlook the "clinical practice points" provided because the doses and indications are listed at the top of the order form. Other factors that may be contributing to inappropriate use include a lack of detailed information on the order form that is necessary to help providers make appropriate decisions and reevaluate their decisions after the initial order.

RECOMMENDATIONS

- Ensure that healthcare providers are aware of the pre-printed IV PPI order form through re-education and promotion.
- Changes to the clinician order form will be considered.
- Implement a 72 hour automatic stop to all intermittent IV pantoprazole orders.

References available upon request

Did You Know...

The MUSC Drug Information Center publishes clinically relevant questions and responses that are received in a Virtual Drug Information (VDI) Database. All MUSC employees have access to VDI. For access, visit https://www.muschealth.com/vdiSearch/Login.aspx? (links are also available on the *Formulary and Drug Information* Web page www.formularyproductions.com/musc).

- Use your NetID login and search by keywords or type of question.
- Information is only as current as the post date on the entry.
- If you do not find what you are looking for, contact the Drug Information Center (2-3896 or druginfo@musc.edu) for assistance.

FORMULARY UPDATE FOR APRIL 2009

In April 2009, The Pharmacy and Therapeutics Committee approved the actions listed below. The formulary effective date was May 18, 2009, unless otherwise stated.

ADDITIONS

Zanamavir (Relenza®), an antiretroviral agent similar to oseltamavir, was added to the formulary temporarily as a result of the Swine Influenza type A (H1N1) outbreak. This was to allow the hospital to stock additional antiretroviral agents effective against the disease in case the outbreak worsens. Once H1N1 virus is contained, zanamavir will be removed from the formulary and oseltamavir will be the sole formulary agent.

Powder for inhalation: 5 mg

Formulary effective date: April 28, 2009

MODIFICATION

In order to increase pharmacy storage space, it was requested that the organization simplify the combination oral contraceptive options available on formulary. For hospitalized patients, these agents are primarily used to control severe uterine bleeding following. Based on utilization data from the past 2 years, all combination oral contraceptive options will be removed from the formulary except for Ovcon® 35, Ovcon® 50, and Lessina™. Hospitalized patients requiring non-formulary combination oral contraceptives will have the option to bring in their own medication or the product will be obtained from one of the ambulatory pharmacies.

The following was removed from the formulary:

- Ethinyl estradiol/levonorgestrel (Portia®)
- Ethinyl estradiol/norethindrone (Junel™ Fe 1.5/30)
- Ethinyl estradiol/norgestrel (Cryselle®)
- Ethinyl estradiol/norgestimate (Sprintec™)
- Ethinyl estradiol/levonorgestrel (Empresse®)
- Ethinyl estradiol/norgestimate (Tri-Sprintec™)

LINE EXTENSIONS

- Acetaminophen 160-mg/5-ml oral suspension, unit-dose cups
- Polysaccharide iron complex (Ferrex® 150; Ferrex® 150 Plus) capsules

DELETIONS

- Antihemophilic factor VIII (Helixate®) 500-unit vial
- Polysaccharide iron complex (Niferex®; Niferex® 150; Niferex® PN) capsules

CHARTS, GUIDELINES, AND ORDER FORMS

Policy C78: Medication Orders* was updated with the following:

- Use of blue or black ink for written orders
- Inclusion of allergy information on all medication orders
- Specific dates must be listed on an order when writing future orders post-op (eg, Post-Op day #1 must be defined)
- Nursing must be notified of any STAT order that has been placed
- Transfer orders expire 24 hours after the time that they were originally written
- Differentiation between manually written orders and CPOE

Policy C126: Expiration Dating* was amended so that Appendix A now summarizes all requirements for the labeling of medications.

- Syringes prepared outside of a pharmacy clean room expires 1 hour after preparation.
- For IV bags prepared outside a pharmacy clean room, administration must begin within 1 hour of preparation and expires 12 hours after administration is initiated.

Policy C117: Medication Labeling* now refers to Policy C126 for expiration date/time requirements for medication labels.

*These policy changes are pending Medical Executive Committee (MEC) approval.