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The Utilization Evaluation of Intravenous Pantoprazole for Stress Ulcer Prophylaxis in a Major Teaching Hospital

Shahriyar Shahbazi Khamas[1], Fatemeh Darvishi[1], Hamidreza Taghvaye-Masoumi[2], Elahe Rafiei[3], Atefeh Jafari[2*]

[1]School of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran.

[2]Department of Clinical Pharmacy, School of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran.

[3]Razi Clinical Research Development Unit, Guilan University of Medical Sciences, Rasht, Iran.

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are one of the first-line drugs for acid-dependent diseases. Inappropriate use of PPIs, especially the Intravenous (IV) formula of pantoprazole, can result in excessive cost. This study aimed to evaluate IV pantoprazole usage's appropriateness and optimize its use in accordance with guidelines at Razi educational and remedial center, Rasht, Iran.

Methods: This cross-sectional study was executed in five months among 344 patients of Razi hospital who received IV pantoprazole for stress ulcer prophylaxis (SUP). Demographic data, route and doses of pantoprazole, risk factors for stress ulcer, and other related medical data were recorded. In addition, the appropriate use of IV pantoprazole was measured according to recommendations arranged by this center and the American Society of Health-System Pharmacists.

Results: Out of 197 patients who received SUP with an appropriate indication, 183 patients (92.9%) were able to tolerate the drug orally, and only 14 patients (7.1%) had an indication for receiving IV pantoprazole. There was a significant difference between patients who received SUP with an indication regarding having or not having an indication for IV pantoprazole (P = 0.007). 5029 vials (96.5%) with a cost of 17,822 US dollars were used inappropriately and imposed an additional cost on the health care system.

Conclusion: This study presented that the majority of IV pantoprazole use in this center was not well-matched with guidelines in most cases, containing appropriate indication and right dosing. In order to prescribe this drug as SUP, it is necessary to be more careful about the criteria for prescribing and conforming the prescribed drug and the prescribed dose to the relevant instructions.

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Introduction

Irrational drug use has become a major concern in health care system management, especially in developing countries, due to financial limitations (1). Rational drug use is built upon the appropriate guidelines and medical needs of patients and has a significant part in the health management (2). Drug use evaluation (DUE) is defined as a persistent platform for assessing the appropriateness of drug indications, dosing, rate and duration of administration, interactions, and monitoring of patients throughout their treatment progress (3). These studies are particularly significant for medications with a narrow therapeutic index or expensive or broadly administered drugs as they would have a significant medical and economic effect on the health care system (4). Thus, DUEs are a valued method for examining the quality and financial side of prescriptions.

Stress ulcer is a form of hemorrhagic ulcer commonly provoked in the gastrointestinal system by unusually high physiological stress such as trauma, organ failure, major surgery, burns, or sepsis. The blood loss due to stress ulcers can rise the length of hospital stay, mortality, and costs. Acid suppression is regularly used to prevent ulcer development, a

*Corresponding Author: Dr Atefeh Jafari
Address: Department of Clinical Pharmacy, School of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran. Tel: +981333486470
Email: atf.jafari@gmail.com

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practice known as stress ulcer prophylaxis (SUP)(5). Proton pump inhibitors (PPIs) are frequently prescribed for patients as SUP. Pantoprazole is a PPI with both oral and intravenous (IV) dosage forms and is the only IV PPI available in Iran. The decision to choose an appropriate dosage form rest on several aspects, like the patient's ability to receive oral medicine, the patient's hemodynamic status in addition to intestinal penetrability, and absorptive volume (6). Currently, there has been a trend concerning overutilization of SUP in hospitalized patients because evidence-based implemented guidelines on who should take SUP in patients are not followed consistently (1, 7, 8).

Inappropriate use of medicine was previously documented in this center while evaluating albumin usage's appropriateness(9). Implementing a rational prescribing guideline led to an increase in the inappropriateness of prescriptions and cost reduction. Inappropriate and unsupervised administration of IV pantoprazole can lead to increased therapeutic cost (wastage), adverse effects associated with injection, and also increasing the occurrence of community-acquired pneumonia (10), spontaneous bacterial peritonitis (11), vitamins and minerals malabsorption (12), bone fractures (13), and clostridium difficile infection (6, 8, 14).

Pharmacists encourage appropriate SUP by preparing and applying therapeutic guidelines and educational courses built upon the best accessible evidence. Clinical pharmacists are professionals in medication use, with their assistance to patient care, enhanced pharmacotherapy outcomes, and cost savings (15, 16). A recent study by Bazan et al., reported that clinical pharmacists' interventions reduced non-adherence to the SUP guideline and delivered a substantial decline in hospital expenses of around $US948 in six months (15). Bearing in mind the 40-fold difference between the price of IV pantoprazole in oral dosage form along with undesirable consequences associated with its inappropriate use and its direct and indirect cost on the health care system, we designed this study to evaluate the appropriateness of IV pantoprazole utilization in accordance with evidence-based guideline at Razi educational and remedial center of Rasht, Iran to optimize drug prescription and administration and decrease treatment cost.

Methods

This study was a prospective cross-sectional five-month study conducted in Razi educational and remedial center, a teaching hospital of Guilan University of Medical Sciences, on patients receiving SUP from March to September 2019. The initial internal guideline for rational prescription and administration of IV pantoprazole was updated and redesigned by the clinical pharmacists of the hospital's pharmaceutical care department in accordance with international guidelines such as the American Society of Health-System Pharmacists (ASHP)(17) and other studies (18-22) (Table 1). In addition, the clinical pharmacists developed a data collection form. In terms of indication for receiving SUP, according to the designed guideline, all patients were divided into two groups: SUP-appropriate + (with an indication of receiving SUP) and SUP-inappropriate (without indication of receiving SUP) and in terms of tolerance to oral administration were divided into two groups IV-appropriate (oral administration intolerance) and IV-inappropriate (oral administration tolerance).

Table 1. Designed for stress ulcer prophylaxis.

Major	Spinal cord injury
	Mechanical ventilation for >48 hours
	Burn more than 35% Body Surface Area
	Coagulopathy (platelet count <50,000 per mm3, an International Normalized Ratio (INR) >1.5, or a partial thromboplastin time (PTT) >2 times the control value.)
	Patients with a history of gastrointestinal ulceration or bleeding within one year before admission
	Head trauma with Glasgow coma scale ≤ 10 or inability to obey simple commands
Minor	Intensive care unit stay for >1 week
	Sepsis
	Hepatic failure
	Occult bleeding lasting for six or more days
	Renal insufficiency
	Heart failure
	Partial hepatectomy
	Prolonged NPO status lasting more than five days
	Multiple traumas with injury severity score (ISS) ≥ 16
	History of NSAIDs use or aspirin in last three months
	Renal or hepatic transplantation
	Head trauma with Glasgow coma scale ≥ 10
	Glucocorticoid therapy (more than 250 mg hydrocortisone or the equivalent)
	Use of antiplatelets or anticoagulants in therapeutic doses

Throughout the study period, a total of 2037 patients received IV pantoprazole. First, a daily list of patients admitted to each ward receiving pantoprazole was received from the Hospital Information System to examine patients. Then, for each ward, the bed number of these patients was given as data separately to Microsoft Excel (Microsoft, Redmond, WA, USA), and then using the formula of INDEX and RANDBETWEEN(23); 30% of these beds were randomly selected. Then, the records of selected patients were assessed. Finally, a total of 620 randomly selected patients were evaluated, of which 276 patients were excluded due to acute gastrointestinal bleeding or diagnosis indicating the need for IV pantoprazole, and 344 patients who, according to the physician's order, received IV pantoprazole for SUP; were recruited in this study. Exclusion criteria were as follows: acute gastrointestinal bleeding or indications requiring IV of pantoprazole for treatment (not prevention) such as dyspepsia, Gastroesophageal reflux disease, Zollinger–Ellison Syndrome, and Helicobacter pylori infection.

Using patient records and patient visits, demographic and clinical information of patients, dose, frequency, and treatment duration with IV of pantoprazole were recorded in the designed data collection form. The appropriateness of the indication, dose, and route administration of prescribed IV pantoprazole, were checked with the designed guideline and patient visits by a clinical pharmacist, then all patients were divided into two groups: SUP-appropriate and SUP-inappropriate. According to the designed guideline, the patient must have at least one major or two minor indications in order to be prescribed IV pantoprazole for SUP. In addition, during the hospitalization, data related to the conversion of IV pantoprazole to other oral or injectable drugs with an indication for SUP (including oral pantoprazole, oral omeprazole, oral or IV ranitidine) was evaluated and followed.

To calculate the cost of treatment and wastage due to inappropriate use of IV pantoprazole, the number of vials consumed and their price were also recorded. As a final point, in order to reduce the effect of variation in the length of hospital stay in patients, the total number of patients-days and the total number of patients-days (inappropriate) for patients with inappropriate use of IV pantoprazole were recorded. The results were used to show the rate of inappropriate use in incidence per 100 days. For this purpose, the total number of patients-days (inappropriate) was divided by the total number of patients-days and then converted to incidence per 100 patients-days.

Data analysis was done using SPSS software (Statistical Package for the Social Sciences, version 25.0; SPSS Inc., Chicago, Illinois, USA). Quantitative results were reported as mean ± SD and qualitative results as a number and percentages. The Chi-square test and fisher were used for data analysis, and P-value <0.05 was considered statistically significant. The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1397.467), and the privacy of the patients was assured.

Results

In this study, out of 344 patients, 172 patients (50%) were female, and 172 patients (50%) were male. Among female and male patients, 71 (48.3%) and 76 (51.7%) did not have an indication for SUP, respectively. The mean age of patients was 59.84 ± 17.72 years, ranging from 14 to 93 years, and most patients (57%) were over 60 years old, and there was a significant difference between the two groups (P = 0.001). The median hospital stays of patients were 13 days and ranged between 2 to 58 days. Baseline demographic and medical details are presented in Table 2. Our study's most frequent major risk factors were coagulation disorder in 54 patients (27.4%), followed by mechanical ventilation in 45 patients (22.8%). Kidney damage in 98 patients (49.7%) and history of NSAIDs and aspirin use in 94 patients (47.7%) were the most frequent minor risk factors.

Table 2. General characteristics and stress ulcer risk factors among study patients

	SUP-appropriate	SUP-inappropriate	P-value
Sex			0.586
Male	96 (55.8)	76 (44.2)	
Female	101 (58.7)	71 (41.3)	
Age			**0.001**
<30	6 (1.7)	16 (4.7)	
30-60	57 (16.6)	69 (20)	
>60	134 (39)	62 (18)	
[+]Polypharmacy			**0.001**
Yes	178 (51.7)	99 (28.8)	
No	19 (5.5)	48 (14)	

Table 2. Continued

History of Gastrointestinal Symptoms			
Yes	42 (12.2)	32 (9.3)	0.92
No	155 (45.1)	115 (33.4)	
Shift of prescription			
Morning shift (08:00-14:00)	102 (29.6)	62 (18)	**0.017**
Evening shift (14:00-20:00)	38 (11)	48 (14)	
Night shift (20:00-08:00)	57 (16.6)	37 (10.8)	
Day of prescription			
Working days	163 (47.4)	138 (40)1	**0.002**
Weekends and official holidays	34 (9.9)	9 (2.6)	
Clinical outcome			**0.001**
Discharge	117 (34)	133 (38.7)	
Death	80 (23.2)	14 (4.1)	
Distribution of patients in each ward			**0.001**
Emergency	64 (18.6)	14 (4.1)	
Internal	49 (14.2)	29 (8.4)	
Nephrology	24 (7)	13 (3.8)	
Urology	8 (2.3)	17 (4.9)	
Poisoning	7 (2)	17 (4.9)	
Intensive care unit	14 (4.1)	7 (2)	
Gastroenterology	7 (2)	12 (3.5)	
Pulmonary	7 (2)	7 (2)	
Infectious disease	9 (2.6)	5 (1.4)	
Endocrinology & Rheumatology	2 (0.6)	12 (3.5)	
Dermatology	4 (1.2)	9 (2.6)	
Surgery	0 (0)	4 (1.2)	
Hematology	2 (0.6)	1 (0.3)	
Clinical status of patients during hospitalization			**0.001**
*SUP-appropriate,#IV-appropriate	11 (3.2)	2 (0.6)	
SUP-appropriate, IV-inappropriate	177 (51.4)	12 (3.5)	
SUP-inappropriate, IV-inappropriate	9 (2.6)	133 (38.7)	

Polypharmacy: taking more than five drugs simultaneously, SUP:stress ulcer prophylaxis, IV:intravenous

One hundred ninety-seven patients (59.8%) had an indication for SUP on the first day of admission. Also, out of 197 SUP patients with an indication, 183 patients (92.9%) were able to tolerate the drug orally, and only 14 patients (7.1%) had an indication for receiving IV pantoprazole (IV-appropriate). There was a significant difference between SUP-appropriate patients regarding having or not having an indication for IV pantoprazole (P = 0.007).

The most inappropriate administration of IV pantoprazole for SUP (SUP-appropriate) occurred in patients with an initial diagnosis of poisoning (68%) and gastrointestinal symptoms (56.9%). On the other hand, the most appropriate administration of IV pantoprazole for SUP-appropriate has been performed in patients with endocrine

problems (87.5%) and heart problems (71.4%), and there was a significant difference between the two groups of SUP-appropriate and SUP-inappropriate indication in terms of initial diagnosis at admission (P = 0.004).

According to our guideline, the correct recommended dose for SUP in patients was 40 mg once daily. According to the patients' records, out of 344 administrations, 213 (61.3%) received the correct dose of 40 mg once daily, and 131 (38.1%) received a dose higher than the guideline (40 mg twice daily). There was no significant difference between the two groups in terms of a history of gastrointestinal symptoms in the past year (P = 0.961)

A total of 5275 vials were consumed, which resulted in a cost of 18,462.5 US dollars. The average number of vials was 12 vials in 11 days at the cost of 42 US dollars, and the range of vials used was between 2 and 93 vials. Out of the total vials, only 183 vials (3.5%) with a cost of 640.5 US dollars have been used with the correct indication and the remaining 5029 vials (96.5%) with a cost of 17,822 US dollars was used inappropriately and imposed an additional cost on the health care system. The total patient-days was 5619, and 3577 patient-days (inappropriate) were recorded for SUP, so inappropriate prescription was 63.7 per 100 patient-days.

Table 3. Detailed costs of intravenous pantoprazole use as stress ulcer prophylaxis.

SUP status at admission	SUP status during hospitalization	No. of vials consumed (%)	Cost (US dollars)	Indication
*SUP-appropriate	SUP-appropriate, #IV-appropriate	147 (2.8)	514.5	Appropriate
	SUP-appropriate, IV-inappropriate	3252 (61.6)	1,1382	Inappropriate
	SUP-inappropriate	162 (3.1)	567	Inappropriate
*SUP-inappropriate	SUP-appropriate, IV-appropriate	36 (0.7)	126	Appropriate
	SUP-appropriate, IV-inappropriate	179 (3.4)	626.5	Inappropriate
	SUP-inappropriate	1499 (28.40	5,246.5	Inappropriate
Overall		5275 (100)	18,462.5	
Appropriate		183 (3.5)	640.5	
Inappropriate		5092 (96.5)	17,822	

* SUP-appropriate: with an indication of receiving SUP, SUP-inappropriate: without indication of receiving SUP
# IV-appropriate: Not able to tolerate oral administration, IV-inappropriate: Able to tolerate oral administration.
SUP:stress ulcer prophylaxis, IV:intravenous

Discussion

PPIs effectively prevent acid-induced damage to the gastrointestinal tract, and the existing guidelines confirm the prescription of these drugs under certain conditions (24). Widespread and inappropriate use of PPIs, even in patients at high risk for gastrointestinal bleeding, causes potential adverse effects and, consequently, no benefit (5, 18, 21, 25). On the other hand, for patients at low risk for gastrointestinal bleeding, the use of PPIs without a proper indication is also harmful. Several studies have been conducted worldwide to evaluate the rational prescription and use of IV pantoprazole in hospitals, which indicate the inappropriate and sometimes unnecessary usage of this drug (1, 18, 20, 21, 26), resulting in a substantial financial burden on the patients and the healthcare system. The results of this study showed that 42.7% of pantoprazole prescriptions for SUP were inappropriate throughout the study, and among the patients who had an appropriate indication for receiving SUP, 92.9% of patients did not have an indication for the IV dosage form. At present, the price of medications is one of the chief portions of the hospital's budget; thus, monitoring medication usage and their rational prescribing will save many hospital costs.

The highest major risk factor with an appropriate indication for SUP was coagulation disorder, and the highest minor risk factors were kidney failure and a history of NSAIDs and aspirin use. Algudah et al., found the highest major risk factor was a history of gastrointestinal bleeding in the past year, and the highest minor risk factors were high-dose corticosteroid use and liver failure (25).

In the current study, 42.2% of the inappropriate prescriptions were in the morning shift, and 93.9% were

on a working day. In a similar study by Craig et al., 57.7% of inappropriate prescriptions were in the morning shift of the workday (27). This may be due to the lack of careful attention of the physician to the existence or lack of appropriate indications for receiving SUP in patients due to the crowded ward during working hours and days compared to other times. In another similar study conducted by Sohrevardi et al., the most inappropriate administrations occurred during night shifts (28).

This study demonstrated that most patients had appropriate indications in the age groups of 30 to 60 years (46.9%) and over 60 years (42.2%). On the other hand, the number of drugs used in 87.8% of patients over 60 years was more than five drugs, leading to the administration of pantoprazole without proper indication for SUP in this age group. However, older patients are more prone to adverse effects of pantoprazole, such as decreased bone density and pelvic bone fractures (8), so these drugs should be prescribed with greater caution.

There was a significant difference in terms of diagnosis at admission (P-value = 0.001) between patients SUP-appropriate and SUP-inappropriate, and the highest prescriptions with inappropriate indication were in patients with a diagnosis of poisoning (68%). The surgical ward had the highest percentage of patients with an inappropriate indication (100%). This finding is similar to the study of Churi et al., and Craig et al., (21, 27).

In the present study, patients were monitored regularly during hospitalization, and among patients who had the appropriate indication for receiving SUP at the time of admission, only 5.6% had the correct indication for receiving IV pantoprazole. Among the rest of the patients in this group, 89.8% of patients continued to take the injectable form of pantoprazole despite the oral tolerance to the drug, and 4.6% of the patients continued to receive pantoprazole for SUP without appropriate indication. In a similar study by Churi et al., 31.1% of patients in the general department of the hospital and 49.83% of patients in the surgical ward continued to receive IV pantoprazole despite changing their clinical status (21).

In this study, the incidence of inappropriate SUP administration was 63.7 per 100 patient-days. In a similar study by Masood et al., The incidence of inappropriate SUP administration was 26.75 per 100 patients-days that showed a high rate of inappropriate use of IV pantoprazole for SUP in this center (20); this high difference compared with our study might be because of high residents and interns workload, lack of proper education, and not paying enough attention to indications. Also, during the 5-month study period, a total of 18,462 US dollars was spent on IV pantoprazole, of which only 640.5 US dollars (3.5%) was with appropriate indications. The total cost of IV pantoprazole with inappropriate indication was equal to 17,822 US dollars; high wastage was also seen in Gharebaghi et al., study, which was conducted on patients in the ICU of a university-affiliated hospital in Urmia (901 US dollars) (26), Moradi et al., directed on patients admitted to a referral hospital in Zabo1,(538 US dollars) (18) and Masood et al., conducted on patients admitted to the intensive care unit of a teaching hospital (2433 US dollars) (20). Worth noting in this study that the cost of the syringes consumed in administration and nursing time required were not included, as the calculation of these expenses exceeded the objectives of this study.

The most common factors for inappropriate prescription of IV pantoprazole as SUP were male gender, old age, taking more than five drugs simultaneously (polypharmacy), history of taking PPIs before hospitalization, and admission in the morning, and initial diagnosis of poisoning. In order to prescribe this drug as SUP, it is necessary to be more careful about the criteria for prescribing and conforming the prescribed drug and the prescribed dose to the relevant instructions. There are several solutions to this inappropriate use, including participation and involvement of pharmacists, especially clinical pharmacists in the treatment process (19, 22, 29), setting up clinical decision support software (30), improving the knowledge of health care professionals (15), and most important of all require medication reconciliation both on admission as well as at discharge for all patients by trained pharmacists (31).

Conducting DUEs without follow-ups has a partial role in improving the rationalization of drug use. So, episodic re-evaluations are recommended to continue the implementation of the SUP guideline. It is also necessary to hold regular meetings with clinicians to provide reports on the implementation of hospital guidelines for correction and following modifications. Creating continuous and regular communication with clinicians to receive feedback and ideas about the designed guidelines will advance this process.

At present, there is no complete guideline or protocol in our country that is based on evidence and accurately states the rational indications for IV pantoprazole consumption as SUP. Another limitation is the small number of patients admitted to each ward during the study period, making it impossible to perform accurate and detailed statistical analyses separately.

This study presented that most IV pantoprazole use in this center was inappropriate and not well-matched with guidelines in most cases, including appropriate indication and right dosing. In order to prescribe this drug as SUP, it is necessary to be more careful about the criteria for

prescribing and conforming the prescribed drug and the prescribed dose to the relevant instructions. In addition, medication reconciliation needs to be implemented to decrease inappropriate SUP continuation on transfer and/or discharge.

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