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Original Article:
Clinical Characteristics of Intravenous Pantoprazole Consumption in Cardiac Intensive Care Unit

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ABSTRACT

Background: Proton Pump Inhibitors (PPIs) are the most common medicine for the treatment and prophylaxis of acid peptic conditions. The inappropriate use of the PPIs, mainly the intravenous form of pantoprazole may lead to excessive cost and unexpected adverse effects.

Objectives: The present study aimed to evaluate the use of intravenous pantoprazole in the International Heart Center in the north of Iran.

Methods: The current retrospective study was performed on 215 patients hospitalized in Fatemeh Zahra Hospital in Sari City, Iran. Patients' demographics, the type and doses of pantoprazole, and other relevant clinical data were recorded from their documentation. The appropriate use of pantoprazole was evaluated according to recommendations provided by Medscape 2020, and UpToDate 2020.

Results: Prescribing PPI was appropriate for 53.5% of the examined patients; however, the majority of intravenous prescription cases were inappropriate (76.7%). Oral PPIs could have been used in 93.5% of the cases; however, they received the parenteral form of pantoprazole. The main cause of pantoprazole prescription in the explored hospital was stress ulcer prophylaxis, with the median 4/18 days used, which internal specialists in most of the cases (45.6%) prescribed.

Conclusion: In the current study, administrating intravenous pantoprazole was inappropriate in most of the cases. As a result of this improper administration, the extensive cost is exposed to the healthcare system, i.e., likely to be unsafe for patients. Accordingly, risk and indication evaluation for the prescription of pantoprazole should be a priority in each patient. Finally, it seems necessary to determine a protocol for PPI prescription per hospital for the rational use of drugs.

Introduction

Drug Use Evaluation (DUE) studies are systematic methods of information gathering to consider drug-related problems, for optimizing drug use patterns in hospitals. DUEs are essential parts of rational medication use and help ensure the appropriate drug use [1, 2]. DUE studies are critical for medicine with a narrow therapeutic index, specific indications for expensive or widely prescribed drugs [3].

A serious complication developed after cardiac surgery or Coronary Artery Bypass Grafting (CABG) is a gastrointestinal disease, especially upper Gastrointestinal (GI) system bleeding; it is an infrequent but potentially lethal case, as these patients undergo anticoagulant therapy [4-7]. Numerous studies demonstrated the incidence and risk factors of upper GI bleeding for post-cardiac surgery [6-9]. The incidence of GI complications fallowed cardiac surgery was approximately 1%-5.5% [10, 11]. Furthermore, the frequency of the stress ulceration was reported to be approximately 0.35%-0.9%, as well as the mortality rate due to acute peptic ulcers after cardiac surgery ranged from 1% to 22% [12-17]. Therefore, it is reasonable to prescribe prophylactic treatment for upper GI diseases in these patients.

Pantoprazole is a Proton Pump Inhibitor (PPI) with oral and Intravenous (IV) dose forms. It seems that both doe forms present equal effects on reducing gastric acid secretion. An appropriate dose form is selected based on the patient's characteristics, such as the ability to take oral medication and hemodynamic status [18]. PPI selection is more important in critically ill patients. This is because an acid-secreting disorder or the prophylaxis of stress-related mucosal injury is more prevalent in these patients [18].

The inappropriate use of PPIs may increases risks, such as acute interstitial nephritis, infection, diarrhea, bone fracture, vitamin deficiencies, and hypomagnesemia [19]. In the cardiovascular setting, previous studies demonstrated that PPIs might increase cardiovascular risks in coronary artery disease patients and clopidogrel consumers [20]. In the general population, current evidence is insufficient to conclude the relationship between PPIs and MI [21]. Using PPIs might be a potential cause of hypomagnesemia; thus, it may aggravate arrhythmias and further complications [21].

According to the literature, the PPIs were indicated for erosive esophagitis, Gastroesophageal Reflux Disease (GERD), gastric ulcer associated with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), dyspepsia, H. pylori eradication, and Zollinger-Ellison (ZE) syndrome (Uptodate, Medscape). Pantoprazole is the only IV PPI existing in Iran; therefore, it was extensively used in hospitals. Adequate and acceptable IV pantoprazole conceptions result in decrease treatment cost, adverse effects related to injection and the incidence of nosocomial pneumonia, Spontaneous Bacterial Peritonitis (SBP), and Clostridium Difficile Infections (CDI) [18]. IV pantoprazole was among the most expensive and most commonly used drugs in our setting; other treatment options, such as oral pantoprazole and oral famotidine are significantly less costly. Thus, this study aimed to evaluate the prescription pattern of pantoprazole in a cardiac hospital to improve medication use.

Materials and Methods

An observational retrospective study was conducted in the Intensive Care Units (ICUs) of Fatemeh Zahra Hospital in Sari City, Iran, from 2015-2016. This study investigated the medical records of admitted cardiac ICU patients receiving IV pantoprazole therapy.

In total, 215 medical records of admitted patients were studied concerning IV pantoprazole prescription. The inclusion criteria of the study were patients over the age of 18 years with IV pantoprazole prescription in cardiac critical settings. The exclusion criteria included patients under 18 years of age and without IV pantoprazole prescription.

The standard criteria for administering IV pantoprazole were determined from medical sources, including Lexi-Comp (based on the latest version of Uptodate software) and Medscape. The patients' demographic data (age, gender, clinical diagnosis, & concurrent disease) and drug usage (drug dose, duration, preparation, administration route, treatment indications, & concomitant medications) were recorded. The study evaluated IV pantoprazole prescription into two principal categories, i.e., "appropriate" and "inappropriate". It was classified as appropriate if it was confirmed to the medical recourse or inappropriate if it was not performed as per the medical recourse.

The obtained data were analyzed in SPSS using descriptive statistics, such as frequency and mean, as well as. two-way non-parametric Analysis of Variance (ANOVA). The significance level was set at $P<0.05$.

Results

The total number of investigated documentation equaled 215. All data records were included for analysis. An overview of the clinical and demographic characteristics of the research participants is presented in Table 1.

Regarding the frequency of comorbidities in our study, most patients reported at least one co-morbidity with their cardiovascular disease; hypertension had the highest frequency, followed by diabetes mellitus. The concurrent diseases in patients receiving IV pantoprazole are presented in Table 2. The details of the physician's specialty who administered the IV pantoprazole among our study cases were as follows: internal specialist: 45.6%, gastroenterologist: 0.5%, cardiologist: 30.2%, and medical assistant: 23.7%. An overview of concomitant medications in patients receiving IV pantoprazole

Table 1. The clinical and demographic characteristics of the research participants

Variables		No.(%)
Gender	Female	107(49.8)
	Male	108(50.2)
Age (y)	35-45	11(5.1)
	46-55	23(10.7)
	56-65	46(24.4)
	66-75	87(40.5)
	>76	48(22.3)
Comorbidity	Hypertension	19(8.8)
	Diabetes mellitus	12(5.6)
	Others (dyslipidemia, stroke, COPD)	5(2.3)
	Hypertension+diabetes mellitus+one of other comorbidity	97(45.2)
	Without comorbidity	82(38.1)
Renal or hepatic impairment	Yes	50(23.0)
	No	165(67.7)
Smoking	Yes	60(27.9)
	No	155(72.1)
Cause of prescription	Prevention	195(91.0)
	Treatment	20(9.0)
Patients GI condition	NPO	14(6.5)
	PO	201(93.5)
Cause of admission	CABG	49(22.8)
	IHD	160(74.4)
	Others (LHD & AVR)	6(2.8)
History of drug allergy	Yes	19(8.8)
	No	196(91.2)

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Table 2. The preparation, route, and administration duration of pantoprazole

Variable		No.(%)
Initiation at admission	IV	143(66.5)
	Oral	72(33.5)
Dose, mg	40	130(60.4)
	80	85(39.6)
Preparation	Water	2(1)
	Normal saline	21(99)
Route of Administration	Bolus	44(20.5)
	Infusion	171(79.5)
Duration of use, day (Mean±SD)		4.28±1.28

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with their reported percentages is illustrated in Figure 1. Screening patients for the potential drug interactions demonstrated that 94 (43.7%) patients took medications, which may interact with pantoprazole. Clopidogrel, an adjunct to Aspirin had the highest frequency, compared to other drugs (86 out of 94 patients). However, only 3.7% of the examined patients required dose adjustment because of drug-drug interactions between pantoprazole and their medications.

In this study, IV pantoprazole was mostly being prescribed for patients with ischemic heart disease, and

Table 3. The frequency of appropriate administration per references for IV pantoprazole

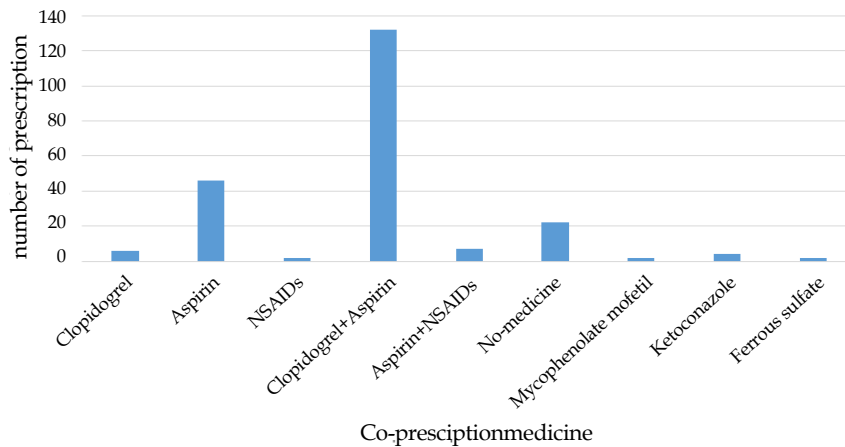| Variables		References Recommendation		Frequency
		Medscape	UpToDate	
Indication, dose, duration	Dyspepsia	40 mg once daily	Oral:20-40 mg once daily for 4 weeks	53.5% for PPIs 23.3% for IV PPIs
	GERD	Oral:40 mg once daily for 8-16 weeks IV: 40 mg once daily for 7-10 days	Oral:40 mg once daily for 8 weeks IV: 40 mg once daily for 7-10 days	
	Zollinger Ellison syndrome	Oral:40 mg daily up to 240 mg IV:80 mg every 8-12hr up to 7 days	Oral:40 mg twice daily IV:80 mg twice daily up to 7 days	
	The prevention of rebleeding in peptic ulcer	-	IV: loading 80 mg, followed by 8 mg/hr or 40 mg every 12 hr for 72 hr Oral: 40 mg once daily for 4-8weeks	
	Helicobacter pylori eradication	-	Oral: 40-80 mg twice daily for 2 weeks	
	Prevention of NSAID induced ulcer	-	Oral:20-40 mg once daily	
	Peptic ulcer disease	Oral: 40 mg once daily for 2-4 weeks	-	
	Stress ulcer prophylaxis in critically ill patients	-	40 mg once daily	
Laboratory test	Mg	Before starting and periodically	Before starting and periodically	100%
	Vitamin B12	-	Before starting and yearly	50%
Drug interaction	Clopidogrel IRON Digoxin Ketoconazole Mycophenolate-mofetil			100%

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Figure 1. Co-prescription medicine with Pantoprazole

CABG. The majority of the examined patients reported no liver or kidney problems. The main indication of IV pantoprazole was preventing stress ulcers. Although nearly all explored hospitalized patients (93.5%) were not NPO (nothing by mouth), they received IV pantoprazole. The details of the preparation and method of administrating pantoprazole are briefly outlined in Table 2. Pantoprazole was administered 40 mg once daily in 90% of the studied cases.

The Mean±SD duration of medicine use in the hospital was 4.28±1.28 days. Approximately, 50% of the pantoprazole prescription were considered acceptable as they fulfilled the clinical guidelines (Table 3). Most patients could tolerate the oral administration; thus, only 23.3% of the IV pantoprazole prescriptions were assumed appropriate.

Discussion

Pantoprazole is the most commonly used PPI in ICUs and the only IV PPI in our settings. The current study evaluated the rational use of pantoprazole injections in cardiac ICUs. The obtained results revealed that the mean dose of pantoprazole use was 40 mg/day. Approximately, 53.5% of the pantoprazole cases were appropriately prescribed based on references. However, IV pantoprazole administration was inappropriate for most of the explored cases (76.7%). Furthermore, the collected data demonstrated that 60% of the patients who received 40 mg pantoprazole daily and 5.39% of the patients who took 80 mg pantoprazole daily had correct administration according to reliable sources. Consistent with our study, another investigation in the north of Iran found that 54% of the cases were rationally given PPIs; however, only 16% of the prescriptions were appropriate for the parenteral form of PPI [22]. One study in Yazd City, Iran found that the majority (63%) of IV pantoprazole administration cases were indicated irrationally [23]. Perwaiz et.al argued that 68.5% of their examined patients were inappropriately prescribed PPI beyond the recommendation of reliable sources [24]. Tze Chia et al. also found that 45.9% of PPI prescriptions in their study were appropriate as stated by the Food and Drug Administration (FDA) [25]. In line with our study, Kaplan et al. demonstrated that approximately 50% of the prescribed IV pan-

Table 4. The frequency of appropriate administration of IV pantoprazole in studies

Reference	Indication for PPIs (%)	Appropriate IV Administration (%)		Duration, Days (Mean)
22	54	16		17
23	60	37		4
24	54.8	31.5		4.5
26	50	Upper GI bleeding	50	9
		Non-upper GI bleedin	33	14
30	58	11		5

toprazole cases were appropriate in high-risk and low-risk groups for Upper Gastrointestinal Bleeding (UGIB & non-UGIB). Moreover, 20% of patients in the UGIB group received correct doses; however, all prescriptions in non- UGIB were correct [26].

The UGIB group in the mentioned study was closer to those of ours. Some results slightly differed from our study, e.g. George et al. in the USA stated that 30% of PPI administrations were based on indication, i.e., conducted on geriatric ambulatory care centers [27]. Additionally, Gamelas et.al documented that 34.9% of patients in an internal medicine ward who were prescribed PPI at discharge, were indicated for receiving [28]. Another study at Malaysian Hospital presented that about 34% of the PPI prescriptions were appropriate, as per guidelines. Although, one-third of prescriptions had no clear reason in Elnaem et al.'s studies, only 19% of prescriptions were irrational per the references [29]. These data might be attributed to differences in settings and patients' conditions and comorbidities. Reviews indicated that the rate of rational use of pantoprazole varies from center to center; however, the rate of appropriate administration of IV PPI is to some extent similar worldwide (described briefly in Table 4).

Reviewing PPIs usage in different settings demonstrated that PPIs were generally prescribed for Stress Ulcer Prophylaxis (SUP) [28]. This is the most frequent indication in our study hospital. The Mean±SD duration of pantoprazole use in this study was measured as 4.28±1.28 days. The duration of pantoprazole treatment was consistent with the references in 95.9% for patients with 40 mg/day for SUP and 89.9% for 80 mg/day doses for treating the bleeding. In line with our survey, Moradi et al.'s results indicated that the SUP was the major cause of IV pantoprazole use after establishing their guideline; the mean duration in their study was approximately 4 days [30].

The main indication for PPI administration in Ahmadi et al.'s study was SUP; however, the duration of the administration was about 17 days [22]. The mean duration of pantoprazole consumption for SUP in Perwaiz's study was approximately 6 days [24]. SUP was the main reason for PPI administration with different mean durations in most studies; however, in Elnaem et al. and Sohrevardi et al.'s studies, gastritis due to concurrent medicines and abdominal pain was the mainspring for PPIs prescription, respectively [23, 29]. Pinto-Sanchez et al.'s systematic review data indicated that PPIs were the first-line treatment for functional dyspepsia due to H. pylori, followed by bleeding management [31].

Studies considered different criteria for evaluating PPI administration; thus, the appropriate prescription rate varied between investigations. However, the overall frequencies of appropriate PPI use never exceeded 50%

[32-35]. Therefore, there is an insistent for improving the use of PPIs in the hospital setting. This was a retrospective study and without guidelines; however, some studies attempted to improve PPI's use. For example, Vazin et.al set checklists for PPIs prescription in their setting. Consequently, the results demonstrated that the total number of IV pantoprazole prescriptions and its relative cost significantly decreased (83.92%) through guidelines determined for pantoprazole prescription [36].

Moradi et al. designed protocols to correctly administer the drug. Accordingly, their study indicated that preparing the protocol reduced the extent of improper and inappropriate prescriptions, as well as the relevant costs. However, as protocol set time passed, the frequency of commitment made by physicians decreased, and less attention was given to the framework [30]. Kaplan et al. also signified decreased prescription of PPI after performing the PPI protocol [26]. Freedberg also addressed a 23% decrease in the prescription rate of PPIs after an electronic alert for IV PPI orders, i.e., associated with a significant reduction in costs [37].

Concerning the short duration of drug use in our study, no adverse effect was observed, or we could not attribute the adverse effect to the drug. In line with the previous case reports, there might be a relationship between PPI use and the incidence of acute hepatitis. However, hepatitis was developed after 4 weeks of PPI consumption, i.e., revealed as the transient elevation of the hepatic enzymes and returned to normal after discontinuing PPIs [38, 39]. The examined patient was monitored for hepatitis. There was no report of acute hepatitis or hepatic enzymes elevation in our study; it might be due to its short-term usage.

Based on these findings, the inappropriate use of pantoprazole was highlighted in most of the explored patients. Improper pantoprazole prescription is among the concerned issue, worldwide. The proper administration will result in quick recovery with lower costs; thus, informing these data to the medical staff may cause more appropriate IV pantoprazole prescription and dose optimization [23]. In addition, involving clinical pharmacists in drug prescribing may improve the quality of pharmacotherapy by decreasing medication errors and drug adverse effects. In conclusion, useful interventions may include regular medication reviews, electronic reminders before prescription, and continuing education for health professionals and consumers [33].

Conclusion

The present study data suggested that pantoprazole prescription was required in approximately half of the explored patients; however, IV administration was in-

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appropriate in most of the examined patients (76.7%), based on references. The main indication for pantoprazole was SUP in high-risk patients, since patients tolerate an oral product, there was no needed to prescribe injectable medication. Therefore, the individual assessment of the risks and indication for the prescription of pantoprazole should be a priority. Eventually, developing a protocol for PPIs prescribing was required per hospital.

The major limitation of this study was its retrospective nature; thus, any restrictions in documenting the patient's condition impacted the obtained results. Furthermore, this study observed patients who received only IV pantoprazole; therefore, different results may be obtained if all routes of pantoprazole administration are evaluated.

Ethical Considerations

Compliance with ethical guidelines

The participants were informed of the purpose of the research and its implementation stages. A written consent has been obtained from the subjects. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished, and if desired, the research results would be available to them. The Helsinki Convention was also observed.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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