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Study on Prescribing Pattern of Proton Pump Inhibitors

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ABSTRACT

Objective: Proton pump inhibitors (PPIs) are still widely used despite increasing reports of adverse events. The objective of this study was to evaluate the pattern of prescription PPIs (proton pump inhibitors) and to monitor any potential drug interactions between these medications and other medications that were being taken concurrently. **Methods:** A prospective observational study was carried out at the MVJ Medical College and Research Centre in Bangalore over a six-month period. **Findings:** Totally, 204 prescriptions were assessed, and the majority of patients were aged 40 to 60 years (34%). The use of distribution-based dosage forms of proton pump inhibitors indicated that capsules were preferred over injections or tablets, with 88 capsules (43%) being utilised compared to 59 injections (29%) and 57 tablets (28 of the 204 prescriptions analysed, 113 (55%) consisting of proton pump inhibitor monotherapy, while 91 (45%) involved proton pump inhibitor combination therapy. Among the 204 prescriptions for PPI monotherapy, pantoprazole was used more frequently, accounting for 107 (98%) prescriptions. This trend was also observed with PPI combination therapy. Esomeprazole-domperidone 50 (53%) was the most commonly prescribed medication combination. Among the 41 prescriptions assessed, 30 (70%) involved drug-drug interactions with proton pump inhibitors (PPIs). The most frequently reported major drug interactions involved Pantoprazole and Methotrexate, whereas the most commonly reported moderate drug interactions involved Esomeprazole and Furosemide. We did not observe any adverse drug reactions (ADRs) and concluded that proton pump inhibitors (PPIs) are reasonably safe for short-term treatment. **Novelty:** The study of drug utilization could assess the prescription pattern of PPIs and identify noteworthy drug interactions in prescriptions. This report on the optimal utilization of proton pump inhibitors can be circulated to the concerned departments to improve patient outcomes.

Keywords: PPI; Prescribing patterns; DI; ADR

INTRODUCTION

PPIs, a class of drugs, are also utilized as prophylactic agents for individuals taking nonsteroidal anti-inflammatory medications)[1] . PPIs are medications used to treat dyspepsia, GERD (gastroesophageal reflux disease), upper gastrointestinal bleeding, and peptic ulcer disease[1]. PPIs commonly approved by the FDA in the United States are esomeprazole, omeprazole, lansoprazole, pantoprazole, and rabeprazole. Although these medications are essential for treating gastric acid-related diseases, they vary in pharmacodynamics, pharmacokinetics, and DI (drug interactions)[1]. PPIs commonly cause mild and self-limiting side effects such as headache, flatulence, constipation, abdominal pain, and diarrhea. Additionally, long-term PPI therapy is associated with an elevated risk of community-acquired pneumonia, hip fractures, Clostridium difficile infection, hypomagnesemia, and gastric carcinoids[2].

PPIs are commonly prescribed to manage ulcers in clinical practice[3,4]. In recent years, there has been a steady rise in PPI prescriptions in both hospital and outpatient settings[1]. Owing to their widespread use in clinical settings, accessibility, potent effectiveness, and extensive marketing efforts, PPIs are frequently prescribed and can be misused[5]. Numerous drug utilisation studies have documented the extensive and inappropriate use of PPIs, which can result in serious and negative health consequences[6,7]. Hence,

additional research is necessary to explore the application of PPIs in the clinical setting.

Although standard guidelines for PPIs prescription have been introduced, previous studies have shown that patients still require appropriate prescription and use of proton pump inhibitors. Available data on PPI prescriptions are restricted to those documented in the literature. Owing to the growing use of PPIs and the necessity to enhance drug safety, further research on the prescription pattern of proton pump inhibitors is necessary. Our objective was to evaluate the patterns of PPI prescriptions in individuals admitted to a tertiary-care hospital. Our secondary aim was to investigate the DI (drug interaction) between PPIs and other drugs prescribed that were taken concurrently, and to evaluate the potential for adverse drug reactions.

METHODOLOGY

An observational study with a prospective design was carried out in the inpatient wards of the Department of General Medicine at M.V.J Medical College and Research Hospital in Bengaluru between September 2016 and February 2017. The study comprised of patients' medical records for those who were prescribed any type of PPIs. Patients with no records of proton pump inhibitor prescriptions in their medical records were excluded. Patient data, including medications, demographics, and clinical information, were collected using a specially designed patient data collection form. Monitoring and documentation of drug interactions (DI) were performed using appropriate databases. Adverse Drug Reactions (ADRs) were assessed based on Preventability & Predictability (Schumock and Thornton scales), severity (Hartwig and Seigel scales), and causality (WHO scale) using an appropriate standard scale, and the data collected were analyzed. IBM SPSS Statistics Version 25.0 was utilized for data analysis. Categorical data are presented as percentages and frequencies.

RESULTS

The general medicine department of the MVJ Medical College and Research Hospital conducted a study over a six-month period, during which 204 patients were examined. The following assessments were performed based on observed data: the majority of the patients in this study were aged 40 to 60 years (34%), 60 to 80 years (33%), and 20 to 40 years (30%). Only 3% of the patients were aged 80 years or above. Of the 204 patients, 123 (60%) were male and 81 (40%) were female. Among the 204 prescriptions observed, capsule 88 (43%) were more frequent, followed by injections 59 (29%) and Tablets 57 (28%). Among 204 prescriptions observed, Oral route 145 (71%) was preferred over Intravenous route 59 (29%). Among 204 prescriptions observed, 113 (55%) were on monotherapy and 91 (45%) were on combination therapy. Among the 109 prescriptions observed, monotherapy with pantoprazole 107 (98%) was seen more frequently than monotherapy with omeprazole 2 (2%). Among 95 prescriptions, combination therapy with Esomeprazole + Domperidone 50 (53%) was prescribed more frequently than Rabeprazole + Domperidone 29 (30%), followed by Pantoprazole + Domperidone 16 (17%). Among the 204 prescriptions observed, instruction on food timing of PPIs (half an hour before food intake) was not mentioned in 70(34%). Of the 204 prescriptions observed, advice on diet was found in the written form in 111 (54%) patients, followed by those given orally 93 (46%). All the 204 prescriptions collected and observed were found legible enough (Table 1).

In 41 prescriptions, drug interactions (DIs) involving PPIs accounted for 70%, while those without PPIs accounted for 30%. Among the DIs with PPIs, 6 were classified as major and 24 as moderate. Major interactions commonly involved Methotrexate and Pantoprazole, whereas moderate interactions were frequently observed with Furosemide and Esomeprazole (Table 2). No adverse drug reactions were reported during the 6-month period.

Table 1: Distribution of patients based on age, gender, dosage form, route of administration, therapy, monotherapy, combination therapy,instructions on Food timings, on diet, (n=204), and legibility of prescription

Variables	n (%)
Age (years) (n=204)	
20 – 40	61 (30)
40 – 60	69 (34)
60 – 80	67 (33)
> 80	7 (3)
Gender (n=204)	
Male	123 (60)
Female	81 (40)
Dosage form (n=204)	
Capsule	88 (43)
Injection	59 (29)
Tablet	57 (28)
Route of administration (n=204)	
Per oral	145 (71)
Intravenous	59 (29)
Therapy (n=204)	
Monotherapy	113 (55)
Combination therapy	91 (45)
Monotherapy (n=109)	
Pantoprazole	107 (28)
Omeprazole	2 (2)
Combination therapy (n=95)	
Esomeprazole + domperidone	50 33()
Rabeprazole + domperidone	29 (30)
Pantoprazole +Domperidone	16 (17)
Instructions (n=204)	
Mentioned	134 (66)
Not mentioned	70 (34)
Diet advises (n=204)	
Written	111 (54)
Oral	93 (46)
Prescription legibility (n=204)	
Legible	204 (100%)

Table 2: Drug Interactions, major drug interactions with PPI and moderate drug interactions with PPI

Drug interactions	n (n=41)	%
DDI with PPIs	30	70%
Other drugs associated with DDIs	11	30%
Interacting drugs	**Severity (n=6)**	**No. of interactions**
Tab. Methotrexate + tab. Pantoprazole	Major	4 (repeated di)
Tab. Methotrexate + cap. Esomeprazole	Major	1
Tab. Clopidogrel + cap. Rabeprazole	Major	1
Interacting drugs	**Severity (n=24)**	**No. of. Interactions**
Tab. Furosemide + Cap. Esomeprazole	Moderate	6 (Repeated DI)
Tab. Furosemide + Tab. Pantoprazole	Moderate	5 (Repeated DI)
Tab. Atorvastatin + Tab. Pantoprazole	Moderate	4 (Repeated DI)
Tab. Clopidogrel + Tab. Pantoprazole	Moderate	2 (Repeated DI)
Tab. Hydrochlorothiazide + Tab. Pantoprazole	Moderate	2 (Repeated DI)
Tab. Furosemide + Cap. Rabeprazole	Moderate	1
Tab. Atorvastatin + Cap. Esomeprazole	Moderate	1
Tab. Atorvastatin + Cap. Omeprazole	Moderate	1
Tab. Escitalopram + Cap. Esomeprazole	Moderate	1
Tab. Ferrous Fumerate + Cap. Rabeprazole	Moderate	1

Table 3: Assessment of major and moderate drug interactions

Assessment of major drug interactions (n=6)				
Interacting drugs	**Mechanism of action**	**Monitoring parameters**	**Clinical Significance (yes/no)**	**Inference**
Clopidogrel + rabeprazole (1 patient)	Combining these medications may reduce the effectiveness of clopidogrel in preventing heart attack or stroke. (Pharmacokinetic DI).	Cardiac monitoring	yes	Preferably avoid this combination. Adjust the dosing interval between 12- 20hours. Safer PPIs like Lansoprazole or pantoprazole may be used.H2RA will be a better Option
Furosemide + esomeprazole (1 patient)	Hypomagnesaemia (Pharmacodynamic DI)	Monitoring of serum magnesium levels is recommended periodically after a prolonged treatment with PPIs	No	Monitor for irregular heart rhythm, palpitations, muscle spasms, Tremors or seizures.
Methotrexate + pantoprazole /Esomeprazole (4 patients)	Increase serum Concentrations of MTX. (pharmacokinetic DI)	Monitor for MTX toxicity - GI toxicity (most common in RA pts)	No	Use of an H2RA Antagonist maybe an appropriate alternative
Assessment of moderate drug interactions (n=24)				
Furosemide/ hydrochlorothiazide +esomeprazole/ pantoprazole/ rabeprazole (14 patients)	Hypomagnesaemia (Pharmacodynamic DI)	Monitoring of serum magnesium level is recommended periodically after a prolonged treatment with PPIs. Monitor for irregular heart rhythm, palpitations, muscle spasms, tremors or seizures.	No	An H2RA (Ranitidine) may be substituted if an interaction is suspected.
Atorvastatin + pantoprazole/ omeprazole/ rabeprazole (6 patients)	Increase the blood levels and effects the atorvastatin also may cause a rare but serious condition called Rhabdomyolysis. (Pharmacodynamic DI)	Monitor for KFT (creatinine kinase levels). Report any unexplained muscle pain, weakness if accompanied by fever or dark colored urine.	No	An H2RA (Ranitidine) may be substituted if an interaction is suspected.
Clopidogrel + pantoprazole (2 patients)	Reduce the effectiveness of clopidogrel in preventing the heart attacks or stroke. (Pharmacodynamic DI)	Close monitoring of therapeutic efficacy of clopidogrel is necessary when administered with pantoprazole.	No	An H2RA (Ranitidine) may be substituted if an interaction is suspected.
Escitalopram + esomeprazole (1 patients)	Increase the blood levels and effects the escitalopram also may cause a rare but serious condition called serotonin syndrome. (Pharmacodynamic DI)	Symptoms of serotonin syndromes includes changes in mental status, mydriasis, shivering, hyperthermia, tremor, nausea, vomiting diarrhea etc.	No	Monitored for serotonin syndrome, if a reaction is suspected, discontinue esomeprazole and use an H2RA instead.
Ferrous fumarate + rabeprazole (1 patient)	Rabeprazole affects the absorption of ferrous fumarate and thus anemic patients on this combination fail to respond to iron replacement therapy. (Pharmacodynamic DI)	Monitor Hb%, MCV frequently.	Yes	After ruling out other causes of anemia, it may be appropriate to continue PPI or continuing administering iron parenterally. H2RA could be used instead.

DISCUSSION

The current investigation analyzed the prescription patterns of PPIs, potential drug interactions of PPIs with other concurrently prescribed medications, and occurrence of suspected ADRs. PPIs continue to be the primary evidence-based treatment for upper gastrointestinal disorders, including Dyspepsia, GERD, PUD (Peptic Ulcer Disease), ulcers induced by NSAIDs, Helicobacter pylori eradication, and hypersecretory disorders such as Zollinger-Ellison Syndrome (ZES)[8]. Various factors can affect PPI prescription patterns. It has been shown that patient-related factors can influence the prescription of PPIs; however, it is also important to consider physician-related factors. Ensuring that physicians adhere to high-quality prescribing practices enhances rationality and ultimately enhances patient care[9]. Therefore, we evaluated the prescription pattern of proton pump inhibitors at a tertiary care facility.

A total of 204 prescriptions were collected and analyzed. The data collected revealed that PPI incidence was higher among individuals aged 40 to 60 years (34%), 60 to 80 years (33%), and 20 to 40 years (30%), with the lowest incidence observed among those aged $\geq$ 80 years (3%). Most patients were aged between 70 and 79 years (17.22%), followed by those aged 10 to 19 years (16.74%) and 50 to 59 years (15.78%)[10].

The distribution based on dosage form could be explained by the fact that capsules enter the bloodstream faster than tablets. In our study, the distribution was based on the PPI dosage form; capsules (43%) were consumed more, followed by injections (29%) and tablets (28%). PPIs exhibit comparable efficacy to intravenous PPIs in individuals suffering from peptic ulcer bleeding[11]. In our study, we found that, out of 204 prescriptions analyzed, the oral route (71%) was favored over the intravenous route (29%). The oral route is the most common method of administration because it is convenient and acceptable for patients.

Monotherapy with PPI is typically prescribed for prophylaxis purposes when co-administered with NSAIDs (such as COXibs, Aspirin, Naproxen, Ibuprofen etc.), Antibiotics (like Amoxicillin, Azithromycin, Cefixime) as well as with Glucocorticoids (like Prednisolone, Hydrocortisone, Methyl Prednisolone etc.)[12]. In the current study, the majority of patients (55%) were prescribed monotherapy rather than a combination therapy (45%). Among those receiving combination therapy, the most common combination was PPI with Domperidone (53%), which was prescribed to patients experiencing symptoms, such as nausea, belching, and fullness of the stomach. Of the 109 prescriptions analyzed, pantoprazole was the preferred choice for monotherapy (98%) compared with omeprazole (2%). All PPIs exhibit comparable efficacy; however, research indicates that esomeprazole may possess greater strength than its counterparts. According to a study by Sheu et al., Esomeprazole has emerged as a formidable PPI in the regulation of gastric acid secretion when juxtaposed with other options[13].

It plays a promising role in the quick control and long-term management of acid peptic disorders, particularly gastroesophageal reflux disease.[13]. In our study, out of 95 prescriptions, a higher percentage included combination therapy with Esomeprazole and Domperidone (53%) than with Rabeprazole and Domperidone (30%), followed by Pantoprazole and Domperidone (17%).

Hatlebakk et al. observed that for optimum daytime gastric acidity control, it is crucial to administer omeprazole or lansoprazole therapy before meals. The recommendation to consume PPIs half an hour prior to eating is vital as it prevents adverse effects on PPI absorption and ensures its effectiveness[14]. Of the 204 prescriptions that we observed, instructions on when to take PPIs were not mentioned in 34% of the prescriptions. Prescription errors frequently occur and may contribute to medical errors; thus, there is a need to critically address the legibility of prescriptions. Adherence by physicians to prescribe good quality medications will minimize errors and eventually enhance patient care[9]. Our study evaluated the legibility of the prescriptions collected and resulted in 100% legibility.

Evaluation of Potential Drug-Drug Interactions in General Medicine Ward of Teaching Hospital, Southern India which defines DIs as pharmacological and clinical outcomes resulting from multiple drugs that are taken simultaneously, compared to when they are used individually. DIs can result in serious life-threatening conditions. Drug interaction (DI) monitoring is not only limited to drugs that are contraindicated but also extends to drugs that require monitoring and dose adjustments. Thus, identifying potential drug interactions (DIs) in clinical settings is essential[15]. Of the 41 prescriptions examined, 30 (70%) involved drug-drug interactions with PPIs. The severity of 6 drug interactions with PPI was rated as major, whereas 24 were considered moderate.

During–5-to-12-year period of continuous proton pump inhibitor therapy, no significant safety issues were identified[14]. Although these medications are generally regarded as safe and have received regulatory approval for long-term use, there are concerns regarding their long-term safety. In recent years, a series of adverse events (AEs) have been observed because of the prolonged use of proton pump inhibitors (PPIs), including an elevated risk of respiratory infections, Clostridium difficile infections, and more recently, bone fractures. However, no adverse drug reactions (ADRs) were observed during the 6-month period.

CONCLUSION

This study on drug utilization assessed the prescription patterns of proton pump inhibitors (PPIs). The study identified drug-drug interactions between PPIs and other medications that were prescribed concurrently. By increasing awareness

among prescribers regarding these significant interactions, we can expect an improvement in patient outcomes.

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