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DRUG USE EVALUATION OF PROTON PUMP INHIBITORS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are the class of drugs that is used indiscriminately, despite the increased reports of adverse events. **Aim:** The study was conducted to evaluate the drug utilization pattern of PPIs in the in-patient department and to assess the rational prescription thereby improving the prescriber awareness and patient care. **Methods:** Prospective observational study on the drug utilization pattern of PPIs was conducted for 3 months in the in-patients of general medicine and surgery departments. We collected 40 cases with PPI prescriptions and evaluated the rationality in the use of PPIs considering the frequency and route of administration, drug interactions, and concurrent medications prescribed. **Results:** In the study, out of 40 patients on PPI, 60% were females and the rest were males. Most of the patients belonged to the age group of 51 - 60 years (12). PPIs were most commonly prescribed for patients with a diagnosis of Respiratory tract infections (42.5%), followed by infectious diseases and gastrointestinal diseases. Pantoprazole was the most commonly prescribed PPI. They were commonly prescribed in the oral route (70%) and on a once-daily basis (62.5%). Antibiotics (50%) and NSAIDs (7.5%) were the most common drugs used along with PPIs. **Conclusion:** PPIs should be used more judiciously and awareness should be created among clinicians in the hospital so that appropriate use of prescriptions with PPIs should improve patient care.

KEYWORDS: Drug utilization, Efficacy, Proton pump inhibitors, Rational use.

INTRODUCTION

Proton Pump Inhibitors (PPIs) are one of the most commonly prescribed category of drugs that cause pronounced and long-lasting suppression of gastric acid production by inhibiting the Hydrogen-Potassium Adenosine Triphosphatase Enzyme system. The National Institute of Clinical Excellence (NICE) guidance recommend indications for prescribing PPIs on the management of Gastro-Esophageal Reflux Disease (GERD) and upper gastrointestinal bleeding (including varices), in the management of Barrett's Oesophagus, Zollinger-Ellison Syndrome, ulcer healing, Helicobacter pylori eradication, prophylaxis of Peptic Ulcer Disease (PUD) for patients taking Non-steroidal Anti-inflammatory Drugs (NSAIDs) / aspirin/steroid, prophylaxis for patients taking anticoagulants, second-line agent for non-ulcer dyspepsia (i.e., dyspeptic symptoms with normal endoscopic findings) and prophylaxis of stress ulcers. Six types of PPIs are approved by the Food and Drug Administration (FDA) which resemble in their pharmacological mechanism of action but differ in the duration of action: Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole, Esomeprazole, and Dexlansoprazole. But nowadays, PPIs became a class of drugs with a high prevalence of being prescribed for unsubstantiated and poorly defined reasons or for conditions where they are not beneficial. In the past few decades, PPIs have eclipsed Histamine type-2 Receptor Antagonist (H2RA) as the most commonly prescribed agents, as the expected symptomatic relief and healing rate of latter is 60% and 50% respectively, which is contradictory to that of the former which is 83% and 78%, especially because of their outstanding efficacy and safety with a maximum recommended treatment duration of 4-8 weeks.

Current guidelines recommend empiric therapy with PPIs for patients suspected of having gastrointestinal related disorders. They are generally well-tolerated, with rare adverse reactions including flatulence, headache, diarrhoea, abdominal pain, and nausea, which are self-limiting or can be addressed by switching to a different PPI. PPIs are generally safe especially when they are used for short term purposes, but recent literature shows an adverse sequelae of long term PPI use including osteoporosis with increased risk of bone fractures,[1] clostridium difficile associated diarrhoea,[2] community – acquired pneumonia,[3] hypomagnesemia,[4] vitamin B12

deficiency, iron deficiency, acute interstitial nephritis, hypergastrinemia, and chronic atrophic gastritis. The use of PPIs has also been suggested to cause changes in the intestinal microbiota composition thus increasing the risk of clostridium difficile infection and chronic liver disease. Due to the same reason PPIs augment unwanted adverse effects of NSAIDs in the small intestine even though they have been shown to minimize NSAID related adverse effects in the stomach. Moreover, discontinuation of PPI treatment has been associated with acid hypersecretion and the development of dyspeptic symptoms in healthy volunteers.

There is growing concern regarding the utilization of PPIs. They are available for the over-the-counter purchase resulting in increased public access, although, over-the-counter PPIs are approved only for short-term management of frequent heartburns, they are also often used for other upper gastrointestinal symptoms including abdominal pain, bloating, and belching. Furthermore, PPIs are used off-label for functional dyspepsia and for long term management of Barrett's esophagus, contributing to overprescription of PPIs for inappropriate indications and their potential overuse, leading to prolonged hospital stay, increased morbidity and mortality.

PPIs are routinely prescribed for the prevention of gastrointestinal bleeding in patients receiving dual antiplatelet therapy (DAPT) (Clopidogrel and Aspirin) after myocardial infarction or percutaneous coronary interventions and stenting. As they are prescribed for long term use in these patients, there is a major concern for clinically significant drug interactions, mainly with clopidogrel by the metabolic inhibition of cytochrome P_{450} enzyme activities. Thus it has been suggested that co-administration of PPIs with DAPT may attenuate the anti-aggregation effects and augment the risk of cardiovascular ischemic events. Moreover, PPIs give rise to a profound and long-lasting elevation of intra-gastric pH, thus reducing the bioavailability of drugs like ketoconazole, when concomitantly administered.

The aim of our study is to evaluate the drug use pattern and rational prescribing of proton pump inhibitors with a focus on drug interactions caused by the PPIs with concomitant drugs.

METHODOLOGY

A prospective observational study was conducted for a period of 3 months from June 2017 to August 2017 in a 600 bedded tertiary care hospital.

Study materials: Patient data collection proforma was prepared for the study. A total of 40 cases were collected and the case sheets were reviewed thoroughly for the evaluation of use of proton pump inhibitors. Route of administration, frequency of administration, conditions for the use of PPIs, drug interactions with PPIs and concomitant drugs administered were considered.

Inclusion criteria: Inpatients of Medicine and Surgery departments who were prescribed with PPIs.

Exclusion criteria: Paediatric and OBG departments, ICU, Casualty.

RESULTS

The study was conducted with 40 patients admitted in the medicine and surgery departments, who were prescribed with PPIs, to evaluate the rational use of the same. In the study, out of 40 patients on PPI, 24 (60%) were females and the rest (40%) were males as shown in Figure 1. Most of the patients prescribed with PPIs belonged to the age group of 51 – 60 years (30%), followed by 41 – 50 years of age (22.5%) (Table 1). Among the 40 patients, respiratory tract infections were the most prominent diagnosis, found in 17 patients (42.5%), followed by other infectious diseases (candidiasis, appendicitis, filariasis, HIV), Urinary tract infections, GI disorders (GERD and Acid peptic disease), liver disorders, anemia and diabetes mellitus (Table 2).

Out of total 40 cases of PPIs prescribed; Pantoprazole was prescribed in 70% of patients, Rabeprazole was prescribed in 27.50% of patients and Omeprazole in 2.50% of patients as shown in Figure 2. Figure 3 shows that 70% of patients were administered with PPIs by parenteral route, 27.50% of patients were administered by oral route and only 1 patient was given by both oral and parenteral route. Majority of patients were prescribed PPIs on a once daily basis (62.50%); only in 37.50% of patients, twice daily therapy was administered as shown in Figure 4.

A total of 50% of prescriptions contained PPIs along with antibiotics (Penicillin and Cephalosporin antibiotics) and 7.5% contained PPIs along with NSAIDs (Tramadol, Paracetamol, Diclofenac, Aspirin). 32.50% of prescriptions with PPIs contained both Antibiotics and NSAIDs. Only 7 moderate drug interactions with PPIs were found in the 40 cases, out of which fluconazole counted for the highest number (Table 3). In the study antibiotics were the most commonly prescribed drugs (48), followed by bronchodialators, antihistamines, NSAIDs/ analgesics, antidiabetics and antacids (Table 4).

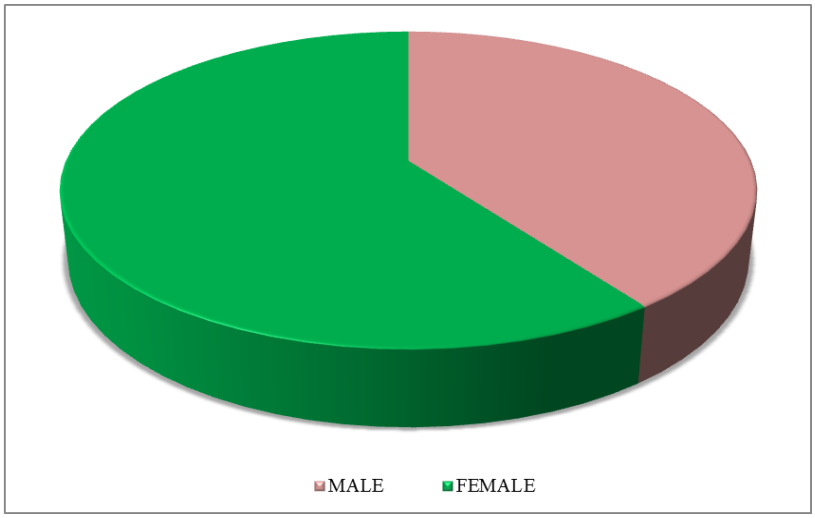

Fig. 1: Gender distribution of patients prescribed with proton pump inhibitors.

Table 1: Age distribution of patients on proton pump inhibitors.

Sr. No	Age group (years)	Number of patients (n=40)
1.	≤ 20	1
2.	21 – 30	4
3.	31 – 40	5
4.	41 – 50	9
5.	51 – 60	12
6.	61 – 70	5
7.	> 70	4

Table 2: Clinical diagnosis of the study population.

Sr. No	Diagnosis	Number of patients (n=40)
1.	Infectious diseases	5
2.	Liver disorders	2
3.	Respiratory tract infections	17
4.	Cardiovascular disorders	2
5.	Gastrointestinal disorders	4
6.	Anaemia	3
7.	Diabetes mellitus	2
8.	Others	5

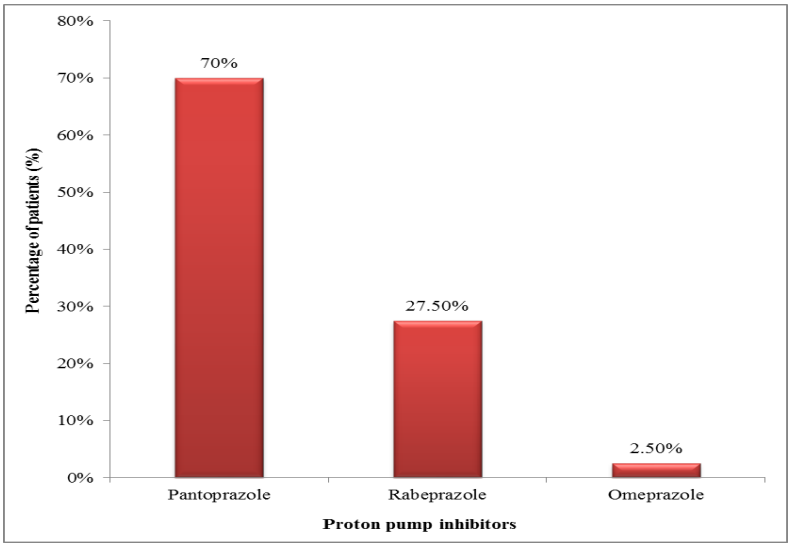

Fig. 2: Proton pump inhibitors used in the study population.

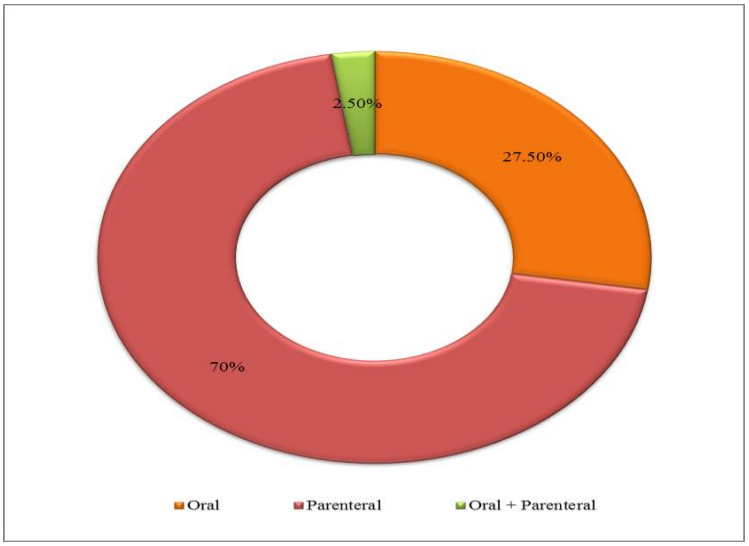

Fig. 3: Route of administration of proton pump inhibitors

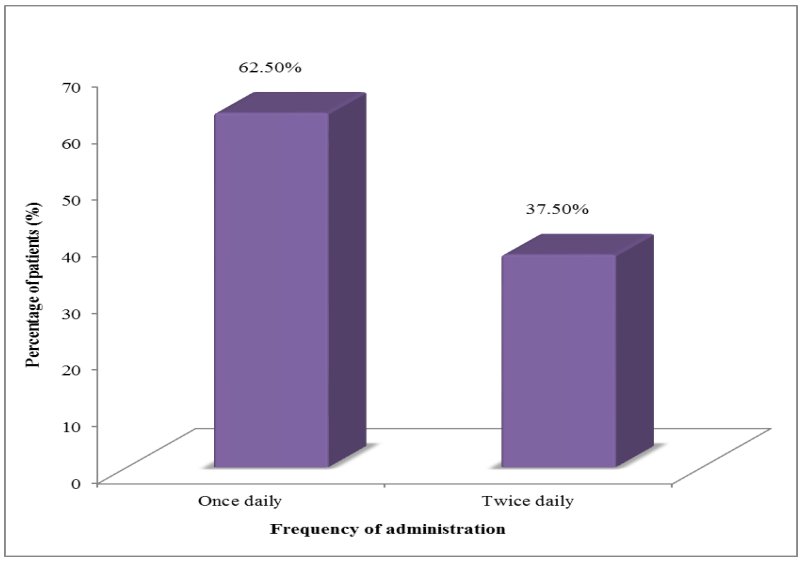

Fig. 4: Frequency of administration of proton pump inhibitors.

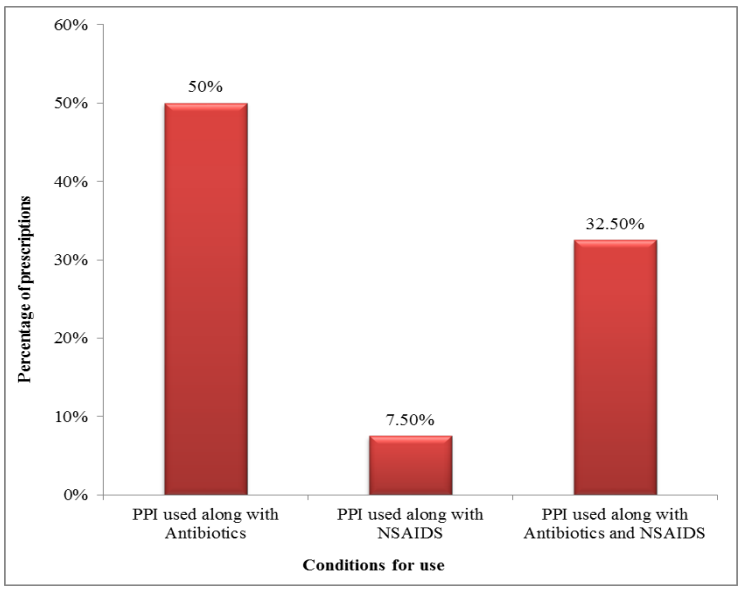

Fig. 5: Conditions for the use of proton pump inhibitors.

Table 3: Moderate drug interactions of PPIs with other drugs.

Sr. No	Interacted drug	Number of patients (n=7)
1.	Propanolol	1
2.	Fluconazole	4
3.	Levothyroxine	1
4	Ferrous fumarate	1

Table 4: Concomitant drugs used along with Proton pump inhibitors.

Sr. No	Concomitant drugs	Number of patients
1.	Antibiotics	48
2.	Vitamin/Mineral supplements	4
3.	Diuretics	9
4.	Dyslipidemic	8
5.	Antiplatelet	5
6.	Bronchodilators	37
7.	Cough/cold formulations and antihistamines	31
8.	Antacids	18
9.	Antihypertensive	15
10.	Anti-TB drugs	5
11.	Antidiarrheal	3
12.	Antiemetic	2
13.	CNS drugs	15
14.	NSAIDS/Analgesics	19
15.	Antidiabetics	19
16.	Antifungal	4
17.	Corticosteroids	10
18.	Others	23

DISCUSSION

The results of the study describe the prescribing pattern of the PPIs as there is a need for thorough evaluation of the usage of the drugs for the indications. In the study, most of the patients were females (60%) who were prescribed with PPIs, which is contrast to the study conducted by Mathew *et al.*,[5] where it was reported that males (55%) were more than females (44%). In our results, patients prescribed with PPIs were more in the age group of 51-60 years (12 patients), which is similar to the study conducted by Rajendra Singh Airee *et al.*,[6] in which out of 100 patients, about 26% belonged to the above mentioned age group. It shows that PPIs are mostly prescribed in geriatric patients as they are more prone to diseases because of their decreased physiology and immunity and altered pharmacokinetic and pharmacodynamics properties.

Out of 40 patients, Respiratory tract infections were most prominent diagnosis found in 17 patients, which is contradictory to the study conducted by Omkar Prasad Baidya *et al.*,[7] where it was reported that for most of the patients PPIs were prescribed for Acid Peptic Disorders (30%). Among the 40 patients, mostly prescribed PPI was Pantoprazole (70%) and least prescribed was Omeprazole, which is almost similar to the study conducted by Lama Madi *et al.*,[8] in which Esomeprazole and Pantoprazole were the most frequently prescribed (34% and 31% respectively). Economically, this is reassuring as Omeprazole is the most expensive drug as compared to the alternatives available in the hospital. Also, Pantoprazole is commonly prescribed in recent years because of its better efficacy and lesser side effects.

In the study, majority of patients were prescribed with the oral therapy of PPIs (70%). The results were in contrast to the study conducted by Neupane *et al.*,[9] in which majority of patients were prescribed with IV PPIs because of patient's physical condition, not able to swallow the drug and use of corticosteroids and NSAIDS. The frequency of PPIs on once daily basis was reported in 62.5% which is more, followed by twice daily basis (37.5%) and it is enough inorder to produce the desirable therapeutic effect in patients. The findings were similar to Nousheen *et al*.[10] Giving PPIs on a twice daily basis for more than a period of 2 weeks may cause undesirable effects.

PPIs are prescribed for many indications like APD, GERD, PUD, ZES and Erosive esophagitis. These are also prescribed along with antibiotics and NSAIDs to prevent the undesirable gastric effects caused by the drugs. In our study, about 50% of patients were prescribed PPIs along with antibiotics and only fewer prescriptions contained PPIs along with NSAIDs. Contradictory studies were reported by Shabbir Rafik Pendhari *et al.*,[11] in which it was reported that about 69% and 53% of prescriptions contained PPIs along with NSAIDs and antibiotics respectively. PPIs cause

significant increases in gastric pH, which may alter the absorption of weak acids or bases. This may lead to various drug-drug interactions with PPIs. Omeprazole is mostly found to interact with Clopidogrel which is major, so co-administration should be avoided in such cases or should be approached cautiously. In the study, only moderate interactions were found with PPIs, mainly with Fluconazole (4) and also with Proponolol, Levothyroxine and Ferrous fumarate. This was in contrast to the study conducted by Rajendra Singh Airee *et al.*,[6] in which one major drug interaction was observed with Clopidogrel, 15 moderate and 4 minor interactions were also found. In the study, antibiotics were the most commonly prescribed concurrent medications (17.4%) which showed similar results to the studies conducted by Nousheen *et al.*,[10] in which antimicrobials were the most commonly prescribed (71%).

CONCLUSION

The drug utilization study that we conducted could assess the prescribing pattern of Proton Pump Inhibitors. We observed a considerable increase of real-world PPI use in a nationwide population setting. The use of PPIs is extensive and increased rapidly than other drugs. Pantoprazole was the most prescribed drug. Our study indicates that PPI are still depended upon by many of the physicians for their ability to produce gastro protective effect, especially when NSAIDs or some antimicrobials are simultaneously administered. This practice is contrary to guidelines and also exposes the patients to avoidable adverse drug reactions. We also identified Drug-Drug Interactions of PPIs with other concurrently prescribed drugs so that this may improve the prescriber awareness on the significant interactions, consequently improving the patient outcome.

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CONFLICTS OF INTEREST

None

ABBREVIATIONS

PPIs - Proton Pump Inhibitors, NSAIDs - Non-steroidal Anti-inflammatory Drugs, GERD - Gastro Oesophageal Reflux Disease, NICE - National Institute of Clinical Excellence, DAPT - Dual Anti-platelet Therapy

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