Prescribing Pattern of Proton Pump Inhibitors

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ABSTRACT

The aim of the study on Prescribing Pattern of Proton Pump Inhibitors in a tertiary care hospital, Bangalore. The objective is to assess the prescribing pattern of proton pump inhibitors and to monitor the drug interactions of PPIs with other concurrently prescribed drugs. A Prospective Observational Study was conducted in MVJ Medical College and Research Centre, Bangalore over a period of 6 months. A total of 204 prescriptions were analyzed during the six months study period. 123 (60%) were males and 81 (40%) were females and majority of the subjects in the study belonged to the age group of 40 – 60 years (34%). The distribution based on dosage form of PPIs, showed that Capsules 88 (43%) were utilized more than injections 59 (29%) and tablets 57(28%). Of 204 prescriptions, 113 (55%) were PPI mono therapy and 91 (45%) were PPI combination therapy. Among 204 prescriptions that were containing PPI monotherapy, Pantoprazole 107 (58%) was seen to be utilized more and among PPI combination therapy Esomeprazole-Domeridone 50 (53%) was the drug combinations that were frequently found to be prescribed. Among the DIs observed in 41 prescriptions, the interactions with PPIs were found to be more (70%) than the ones without. The commonly occurring Major DIs were with Methotrexate and Pantoprazole and the commonly occurring Moderate DIs was Furosemide with Esomeprazole. The studies that we conducted conclude that PPIs are relatively safe short term treatment. The drug utilization study that we conducted could assess the prescribing pattern and significant Drug Interactions in the prescriptions. A report on rational use of PPI was prepared and circulated to concerned department for the better patient outcomes.

Keywords: Prescribing patterns, PPI, DI.

INTRODUCTION

Proton Pump Inhibitors (PPIs) remain the leading evidence based therapy for upper Gastro intestinal disorders, including Gastro-Esophageal Reflux Disease (GERD), Dyspepsia, Peptic Ulcer Disease (PUD), Non-Steroidal Anti Inflammatory Drugs (NSAIDs)-induced ulcer, eradication of Helicobacter pylori (H. pylori), and hyper secretory disorders such as Zollinger-Ellison Syndrome (ZES).1 They are now among the most widely prescribed drugs worldwide because of their outstanding safety and efficacy and thus increasing its availability Over The Counter (OTC).2 Recent observational studies showed that PPIs are the most commonly used prophylactic agents in the ICU.1

PPIs inhibit the proton pump (H+/K+ ATPase) in the parietal cells of the stomach. PPIs accumulate in the secretory canalicus of the parietal cells where they are protonated to a cationic sulfonamide. This then binds to the sulfhydryl group on the proton pump and provides acid suppression for 24-48 hours.3 They may achieve a faster healing rate than H2-receptor antagonists (H2RA). PPIs are potent at maintaining gastric pH between 3.5 and 5.0 may minimize the risk of gastric mucosal injury.4

For most indications other than gastro protection and severe reflux disease, PPIs should only be used for 4–8 weeks, but it is known that use of PPIs is generally much longer.5 Proton pump inhibitors are usually prescribed as a continuous once or twice daily regimen; however, there are indications that patients tend to use PPIs as needed. It may reduce effectiveness especially in patients requiring chronic treatment for erosive oesophagitis.6,7

PPIs are generally well tolerated. The most common adverse reactions seen in adults are flatulence, diarrhea, nausea, abdominal pain, and vomiting. The use of PPIs has also been associated with drug interactions, malabsorption of iron, nutrients and vitamins, hypomagnesaemia, and Clostridium difficile-associated diarrhea (CDAD). Non-judicious PPI use is a matter of great concern in the elderly who often have multiple co morbidities and are taking multiple medications and hence are at risk. Therefore, inappropriate PPI use may lead to increasing healthcare costs, morbidity, and even mortality.8,9 Two studies recently suggested that PPI use may increase the risk for Community Acquired Pneumonia (CAP). A proposed mechanism is increased bacterial colonization in the Upper Gastro Intestinal Tract (GIT) due to gastric acid suppression.10,11

Clinically significant DIs with PPIs are rare. Chronic acid suppression can minimize the effectiveness of any medication requiring acidic environment for absorption. Few commonly prescribed drugs that are affected by acid suppression are digoxin, ampicillin esters, ketoconazole, iron salts, atazanavir.12 For individuals with a history of...
Acute Coronary Syndrome (ACS), PPIs appear to reduce the efficacy of Clopidogrel, an antiplatelet agent used to reduce the risk for subsequent ischemic events. A leading hypothesis is that PPIs compete for and inhibit the clopidogrel-activating hepatic isoenzyme, CYP2C19, thereby interfering with clopidogrel capacity to prevent clot formation in subjects at risk for coronary thrombosis and Myocardial Infarction (MI).

Several factors might influence the prescribing patterns of PPIs. It has been demonstrated that patient related factors have some impact on the prescribing of PPIs, but physician related factors might be of importance as well. Adherence by the physicians to good quality prescribing will improve the rationality and ultimately improve patient care. Therefore we aimed to study on the prescribing pattern of proton pump inhibitors.

MATERIALS AND METHODS

Study design
Prospective Observational Study

Study period
September 2016-Feb 2017

Study population
204

Inclusion criteria
Patients prescribed with any type of PPIs in the in-patient department of general medicine for any chronic/ acute/ prophylaxis purpose.

Exclusion criteria
Patients who are uncooperative or not willing to participate.

Study site
Department of General Medicine MVJ Medical College and Research Hospital, Hoskote, Bengaluru-562114

Human ethical clearance
Human ethical clearance was obtained for carrying out the research work from Ethical Committee of MVJ Medical College & Research Hospital, Hoskote with ethical clearance approval number - Central Research/MJV MC & RH/07/2017

Study method
A prospective observational study was conducted in the department of General Medicine, (Inpatient wards) in M.V.J medical college and research hospital. The human ethical clearance is obtained before conducting the study. Before enrolling the subjects, Informed Consent was obtained and they were informed regarding the purpose of the study. The confidentiality of the subject information was assured. The patients who are satisfying study criteria are enrolled into the study. Cases that are prescribed with PPIs are included and patient information such as demographic, medication and clinical data is collected in specially prepared patient data collection form. Drug Interaction (DI) will be monitored and documented using appropriate data base. Adverse Drug Reaction (ADR) will be assessed based on the Causality (WHO scale), Severity (Hartwig's and Seigel scale) and Preventability & Predictability (Schumock and Thornton scale) by using the appropriate standard scales. The data was collected and analyzed.

Statistical analysis
The data collected was collated, tabulated and summarized. Results will be depicted in the form of percentage and graph.

RESULTS AND DISCUSSION

The present study examined the Prescribing pattern of PPIs, the drug interactions of PPIs with other concurrently prescribed drugs. Adherence by the physician to good quality prescribing will improve the rationality and ultimately improve patient care. In view of these facts, we aim to evaluate the study of prescribing pattern of Proton Pump Inhibitors in a tertiary care hospital.

A total of 204 prescriptions were collected and observed. The following evaluations were made from the observed data. In our study the incidence of PPI use was found more in the age group 40 – 60 years (34%), 60 – 80 years (33%) and 20 – 40 years (30%) followed by 80 years and above (3%). In a study conducted by Nasrin S. et al., most of the patients were observed from the age group between 70 – 79 years old (17.22%) and next from the age group 10 – 19 years (16.74%) follows with 50 – 59 years (15.78%). (Fig 1)
A study conducted by K. K. F. Tsoi et al compared the clinical outcomes of oral PPIs vs. intravenous PPIs in patients with peptic ulcer bleeding and concluded that oral PPIs demonstrate a similar effectiveness to intravenous PPIs among patients with peptic ulcer bleeding. Among 204 prescriptions observed in our study, Per Oral route (71%) was preferred over Intravenous route (29%). Per Oral route of administration is the most widely used because of the convenience and acceptability for patients. According to a study done by Mayet A Y, monotherapy PPI is usually given for prophylaxis purpose while co-prescribed with NSAIDs (Aspirin, COXibs, Ibuprofen, Naproxen etc), Antibiotics (Azithromycin, Amoxicillin, Cefixime) and Glucocorticoids (Methyl Prednisolone, Hydrocortisone, Prednisolone etc). In our study, patients were more on monotherapy (55%) than combination therapy (45%).

Combination therapy of PPI with Domperidone (53%) was utilized in those cases were the patients had complaints of Nausea, Belching, Fullness of stomach etc. Among 109 prescriptions collected and observed, monotherapy with Pantoprazole (98%) was seen more than the ones with Omeprazole (2%).

All the PPIs have similar potency, although studies suggest that that Esomeprazole maybe more powerful than others. In the study conducted by B S Sheu et al., Esomeprazole is a potent PPI when compared with others in terms of controlling gastric acid secretion. It has a promising role for the quick control and longer maintenance of acid peptic diseases, especially for the gastro-esophageal reflux disease. In our study, Among 95 prescriptions analyzed, combination therapy with Esomeprazole – Domperidone (53%) was seen prescribed more than Rabeprazole – Domperidone (30%) followed by Pantoprazole – Domperidone (17%).

When therapy with omeprazole or lansoprazole is indicated, medication should be taken before a meal for optimal control of daytime gastric acidity. The instruction to take PPIs half an hour before food is essential because otherwise, it adversely affects the PPI absorption and causes it to be ineffective. Out of 204 prescriptions that we observed, the instruction on when to take PPIs was mentioned in majority of the prescriptions (66%).

A study was done by Manisha S. Bhosale et al on Analysis of completeness and legibility of prescription orders and the results demonstrate that prescription error frequently occur and may contribute to medical error and thus there is a need to critically address the legibility of prescription.. The study that we conducted observed for legibility of the prescriptions collected and resulted in 100% legibility. A study was conducted by Akram Ahmad et al on “Evaluation of Potential Drug - Drug Interactions in General Medicine Ward of Teaching Hospital” in Southern India which defines DIs as pharmacological and
clinical outcomes resulted from simultaneous use of different combinations of drug as compared to their use alone. These DIs could result in serious life threatening conditions. DI monitoring is not only applicable for those drugs which are contraindicated, but also the ones requiring monitoring and dose adjustment. Therefore, it is essential to identify possible DIs in clinical settings. Among the drug interactions observed in 41 prescriptions, interactions with PPI (70%) were found more than the ones without PPIs (30%). Out of the drug interactions observed with PPI, 6 were major and 24 were moderate. The Table 1 and Table 2 depicts the list of major and moderate drug interactions observed during our study, along with their assessment.

Table 1: List of Major Drug Interactions with PPI

<table>
<thead>
<tr>
<th>SL.NO</th>
<th>Interacting Drugs</th>
<th>Severity</th>
<th>No. of Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tab. Methotrexate + Tab. Pantoprazole</td>
<td>MAJOR</td>
<td>4 (Repeated DI)</td>
</tr>
<tr>
<td>2.</td>
<td>Tab. Methotrexate + Cap. Esomeprazole</td>
<td>MAJOR</td>
<td>1</td>
</tr>
<tr>
<td>3.</td>
<td>Tab. Clopidogrel + Cap. Rabeprazole</td>
<td>MAJOR</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2: List of Moderate Drug Interactions with PPI

<table>
<thead>
<tr>
<th>SL.No</th>
<th>Interacting Drugs</th>
<th>Severity</th>
<th>No. of Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tab. Furosemide + Cap. Esomeprazole</td>
<td>Moderate</td>
<td>6 (Repeated DI)</td>
</tr>
<tr>
<td>2.</td>
<td>Tab. Furosemide + Tab. Pantoprazole</td>
<td>Moderate</td>
<td>5 (Repeated DI)</td>
</tr>
<tr>
<td>3.</td>
<td>Tab. Atorvastatin + Tab. Pantoprazole</td>
<td>Moderate</td>
<td>4 (Repeated DI)</td>
</tr>
<tr>
<td>4.</td>
<td>Tab. Clopidogrel + Tab. Pantoprazole</td>
<td>Moderate</td>
<td>2 (Repeated DI)</td>
</tr>
<tr>
<td>5.</td>
<td>Tab. Hydrochlorothiazide + Tab. Pantoprazole</td>
<td>Moderate</td>
<td>2 (Repeated DI)</td>
</tr>
<tr>
<td>6.</td>
<td>Tab. Furosemide + Cap. Rabeprazole</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>7.</td>
<td>Tab. Atorvastatin + Cap. Esomeprazole</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>8.</td>
<td>Tab. Atorvastatin + Cap. Omeprazole</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>9.</td>
<td>Tab. Escitalopram + Cap. Esomeprazole</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>10.</td>
<td>Tab. Ferrous Fumarate + Cap. Rabeprazole</td>
<td>Moderate</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3: Assessment of Moderate Drug Interactions

<table>
<thead>
<tr>
<th>No</th>
<th>Interacting Drugs</th>
<th>Mechanism of action</th>
<th>Monitoring Parameters</th>
<th>Clinical Significance (Y/N)</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>FUROSEMIDE/HYDROCHLORTHAZIDE+ ESOMEPRAZOLE/PANTOPRAZOLE/RABEPRAZOLE</td>
<td>Hypomagnesaemia(Pharmacodynamic DI)</td>
<td>Monitoring of serum magnesium levels is recommended periodically after a prolonged treatment with PPIs. Monitor for irregular heart rhythm, palpitations, muscle spasms, tremors or seizures.</td>
<td>NO</td>
<td>An H2RA (Ranitidine) may be substituted if an interaction is suspected.</td>
</tr>
<tr>
<td>2.</td>
<td>ATORVASTATIN+PANTOPRAZOLE/ OMEPRAZOLE/RABEPRAZOLE</td>
<td>Increase the blood levels and effects of atorvastatin also may cause a rare but serious condition called Rhabdomyolysis. (pharmacokinetic DI)</td>
<td>Monitor for KFT (creatinine kinase levels). Report any unexplained muscle pain, weakness if accompanied by fever or dark colored urine.</td>
<td>NO</td>
<td>An H2RA (Ranitidine) may be substituted if an interaction is suspected.</td>
</tr>
</tbody>
</table>
3. CLOPIDOGREL+ PANTOPRAZOLE  
Reduce the effectiveness of clopidogrel in preventing heart attacks or stroke. (pharmacokinetic 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.

4. ESCITALOPRAM+ ESOMEPRAZOLE  
Increase the blood levels and effects of Escitalopram also may cause a rare but serious condition called Serotonin syndrome. (pharmacokinetic DI)  
Symptoms of Serotonin syndrome 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.

5. FERROUS FUMERATE+ RABEPRAZOLE  
Rabeprazole affects the absorption of ferrous Fumurate and thus anemic patients on this combination fail to respond to oral iron replacement therapy. (pharmacokinetic DI)  
Monitor Hb%, MCV frequently.  
YES  
After ruling out other causes of anemia, it may be appropriate to discontinue PPI or consider administering iron parenterally. H2RA could be used instead.

S. E. Attwood et al studied on “Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions” and aimed to understand the safety of long-term PPI therapy with omeprazole and esomeprazole. Their study concluded that no major safety concerns arose during 5–12 years of continuous PPI therapy. Although these drugs are considered safe and have been approved for long term use, some long term safety concerns have been raised. In recent years, potential AEs like increased risk of respiratory infections, Clostridium difficile infections and most recently bone fractures have been identified with long term PPI use. However, the study that we conducted did not observe any ADRs during the 6 month period. Thus we could conclude that PPIs are relatively safe short term treatment for gastro intestinal conditions.

**CONCLUSION**

The drug utilization study that we conducted could assess the prescribing pattern of Proton Pump Inhibitors. We also identified Drug-Drug Interactions of PPIs with other concurrently prescribed drugs and could improve the prescriber awareness on the significant interactions, consequently improving the patient outcome.

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