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Research article

## USE OF PROTON PUMP INHIBITORS IN GENERAL PRACTICE: IS IT RATIONALE?

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### ABSTRACT

**Background:** The incidence of improper use of PPIs varies from 40-70% in various studies. Initiation and the continuous use of these drugs without correct indications will result in significant cost to the patient. The present study was planned with the aim of finding out the rational use of PPIs in the in patients of a rural tertiary care hospital. **Objectives:** To assess indications of use of PPIs along with their dose, frequency, rationality of treatment, safety and efficacy. **Methods:** Prospective observational drug-utilization study of PPIs was conducted for two months in the inpatients of General Medicine and General Surgery wards. The sample size of study was (n=100). The case sheets of the patients were reviewed for PPIs prescription and relevant data was taken. A five point Likert scale with validated Reflux Disease Diagnostic Questionnaire (RDQ) having 12 items was used for evaluating symptoms score for assessing efficacy of PPIs. **Results:** A total of 46.72% inpatients were on proton pump inhibitors, in surgery(47.52%) and medicine wards (46.01%). The indications for PPIs therapy were acute gastritis (4%), Gastro Esophageal reflux disease (5%), Duodenal ulcer(1%), co-administration with Non Steroidal Anti-Inflammatory Drugs(32%). PPIs were prescribed irrationally in 58 % of patients without any valid indication. The incidence of polypharmacy was high, average number of drugs per prescription was 4.93. Antimicrobials were the most common drugs used in (71%). **CONCLUSION:** Proton pump inhibitors should be used more judiciously and awareness should be created among the clinicians in the hospital so that appropriate prescription of PPIs will improve the patient care at low cost.

**Keyword:** Proton pump inhibitors, General practice, Rationale

### INTRODUCTION

Proton pump inhibitors (PPIs) are a group of drugs that cause pronounced and long-lasting reduction of gastric acid production. They are most potent gastric acid suppressing drugs currently in clinical use.<sup>1</sup> PPIs irreversibly inhibit the gastric H<sup>+</sup>-K<sup>+</sup> ATPase pump also known as proton pump and reduce both basal and stimulated gastric output. Currently the PPIs available in India are omeprazole, esomeprazole, pantoprazole, rabeprazole and lansoprazole. PPIs are used therapeutically in active ulcers, Zollinger-Ellison syndrome, Gastro oesophageal Reflux

Disease(GERD), GI bleeding, dyspepsia from NSAID's and along with antibiotics for helicobacter pylori.<sup>2</sup> PPIs are also given prophylactically along with NSAID's or Steroids in patients with history of peptic ulcer / previous GI bleed / elderly patients.<sup>3</sup> Proton pump inhibitors have been demonstrated to be safe and well tolerated drugs but short term adverse effects like headache, dizziness, diarrhoea, fatigue, rashes and abdominal pain have been reported in 5% of the patients taking proton pump inhibitors.<sup>4,5</sup> Chronic therapy of PPIs carries an increased risk of bacterial enteritis due to decreased gastric acidity

allowing colonization of ingested pathogens and also infection with *clostridium difficile*.<sup>6,7</sup> long term use of PPIs have also been associated with increased risk of hip fractures, and community acquired pneumonia.<sup>8,9</sup> In setting with low rate of such infections benefit of PPI therapy outweighs the risk developing it.<sup>10</sup> Polypharmacy can also make the elderly patients more likely to confuse their use of medication schedule.<sup>11</sup> Such risks are worth taking for life saving drugs that are clearly indicated, but prescribing PPIs that may not be clinically necessary can put patients at risk of complications.

Inspite of the above mentioned concerns with PPIs, they have become one of the most commonly prescribed medicines worldwide. Some reports suggest that upto 60% of patients suffering from dyspepsia are on drugs like PPIs without proper indication.<sup>12,13</sup>.

PPIs take longer time to provide symptom relief than H2 blockers or antacids. For sporadic dyspepsia, and immediate symptoms relief agents other than PPIs will provide greater patient satisfaction and better clinical outcomes.<sup>14</sup>

The prescriptions for the PPIs have increased consistently over the past years. Many drug utilization studies have reported widespread use of PPIs and that are outside the current prescribing guidelines.<sup>15,16</sup> The incidence of improper use of PPIs varies from 40-70% in various studies.<sup>17-19</sup>

Initiation and the continuous use of these drugs without correct indications will result in significant cost to the patient. The significance of rational use of drugs can be described by WHO definition which states that rational use of drugs require that, patients receive medications appropriate to their clinical needs in doses that meet their own individual requirement for an adequate period of time at lowest cost to them and their community.<sup>17</sup>

Hence in this present scenario, where the use of PPIs is overwhelming, the present study is planned to know the rational use of PPIs in the in patients of General Surgery and General Medicine wards of a rural tertiary care hospital.

### Objectives

- To assess the indications of PPIs usage
- To find out percentage of irrational prescriptions with PPIs (Improper prescriptions without justified indication)
- To assess the frequency of usage of PPIs along with their dosage.

- To assess the safety, efficacy and cost effectiveness of PPIs.

### METHODOLOGY

The study was conducted in the inpatient wards of General medicine and General surgery in Kamineni Institute of Medical Sciences (KIMS), Hospital in collaboration with the Department of pharmacology after taking permission from Institutional Ethics Committee. It was a prospective observational study conducted during the period of June 2013 to August 2013. Patients of either sex, admitted into the inpatient wards of General Medicine and General Surgery in KIMS hospital, Narketpally, between the age group of 20-70 yrs were included in the study. Informed consent was taken from all the patients. Patients not willing to give consent were excluded from the study. The sample size for the study was (n=100).

The demographic data and the detailed history of patient regarding past, present, family, personal and drug history was taken. The other details like the present diagnosis, reason for the present admission, any investigations done to confirm the diagnosis, like endoscopy etc were also noted. The number of drugs, dosage form, frequency and duration of medications the patient is kept on were also taken. Patient were inquired regarding improvement in the symptoms or any adverse drug reactions during the present stay. A five point Likert scale with validated Reflux Disease Diagnostic Questionnaire (RDQ)<sup>20</sup> having 12 items was used for evaluating symptoms score for assessing efficacy of PPIs. This questionnaire was filled by personal interview of the patient on inclusion in the study and on discharge of the patient from hospital. The questionnaire had maximum scoring of 40 and minimum of 12 depending on severity of symptoms like epigastric pain, bloating, vomiting, nausea, heart burn, belching, anorexia etc.<sup>21</sup> Inquiry regarding the adverse or untoward events occurring during the therapy with PPIs was also made from patients included in the study. The cost analysis of the PPIs was done by taking into consideration the available PPIs in the hospital and used in the study. Rationality of the prescription was assessed according to criteria mentioned in previous studies.<sup>16,18,22-27</sup>

### RESULTS

Total 214 case sheets were reviewed, 101 from surgery department and 113 from medicine department over a

period of two months. Out of these 214 cases 100 (46.72%) were on proton pump inhibitors. 47.52% inpatients of surgery wards and 46.01% of inpatients in medicine wards were on proton pump inhibitor therapy as shown in Table 1.

**Table1:** Department wise distribution of patients on Proton pump inhibitors

Department	No. of patients on PPIs	No. of case sheets reviewed	patients on PPIs (%)
Surgery	48	101	47.52
Medicine	52	113	46.01
<b>Total</b>	<b>100</b>	<b>214</b>	<b>46.72</b>

Z=0.442, Hence no significant difference in the prescription of PPIs between the Departments (test for difference between two proportions). Out of 100 patients on proton pump inhibitors majority of them 41% were middle aged between 41-60 years age group, and 61% were males and 39 % females shown in Table 2 and Table 3.

**Table 2:** Age wise distribution of patients on proton pump inhibitors

Age	% of Patients
20-40	44
41-60	41
60 and above	15

**Table 3:** Gender Distribution of patients on proton pump inhibitors

Gender	% of patients
Male	61
Female	39

Z= 4.5081, Hence significant difference in the prescription of PPIs between males and females

**Table 4:** Indications for prescribing PPIs

S.No	Indication	% of patients
1.	Acute Gastritis	4
2.	Duodenal ulcer	1
3.	With NSAIDS	32
4.	GERD	05
5.	Others	58

4% of patients with acute gastritis , 5 % of patients for Gastro Esophageal Reflux Disease (GERD) , 1% Duodenal ulcer , 32 % of patients along with Non Steroidal Anti-Inflammatory Drug and 58 % of patients were prescribed PPIs for other reasons and were neither on NSAIDS nor were having any

symptom related to GERD or acid peptic disease as shown in Table 4. Oral therapy with PPIs was prescribed in 70 % of patients and intravenous PPIs in 30% of patients. The intravenous PPI used in all these patients was Pantoprazole 40 mg given once daily early in the morning.

Majority of the patients were prescribed PPIs once daily 97% only in 3% of the patients Twice daily therapy was administered. As shown in Table 5and Table 6.

**Table 5:** Route of administration of PPI

Route	% of patients
Oral	70
Intravenous	30

**Table 6:** frequency of administration of PPIs

Frequency	% of patients
Once daily	97
Twice daily	03

### Concomitant drugs

The incidence of polypharmacy was high all the patients in the study were prescribed multiple drugs. Average number of drugs per prescription was 4.93. Antimicrobials were the most common drugs used in (71%) patients followed by non steroidal anti-inflammatory drugs and multivitamin preparations in 32% patients as shown in Table 7.

**Table 7:** Concomitant drugs used along with Proton pump inhibitors

S.No	Drugs used	patients %
1.	Antimicrobials	71
2.	NSAIDs	32
3.	Multivitamin preparations	32
4.	Calcium and vitamin D	07
5.	Antihypertensives	09
6.	Vitamin C	10
7.	Antidiabetics	03
8.	Antiemetics	13
9.	Antiplatelets	03
10.	Purgatives /laxatives	02
11.	Corticosteroids	01
12.	Diuretics	03
13.	Antiepileptics	01
14.	Antacids	03
15.	Antimalarial	04
16.	Oral Iron therapy	05
17.	Hypolipidemics	03
18.	Tramadol	22

Majority of the patients 88% were having a low Likert score of < 20, prior to start of therapy only 12 % of the patients were having significant symptoms (Likert score above 21) related to Acid peptic disease or GERD as shown in Table 9.

**Table 8:** Categorization based on likert scale

Likert scale score	% of patients at onset of therapy	% of patients at discharge
12	47	73
13-20	41	22
21-30	07	05
Above 30	05	00

**Table 9:** Likert Score of patients at start of therapy with PPIs and at discharge (Mean  $\pm$ SD)

	Likert score (Mean $\pm$ SD)
At start of therapy	15.15 $\pm$ 5.28
At discharge	12.98 $\pm$ 1.90

Z Value= 3.86, Hence significant difference in the Likert score demonstrating efficacy of PPIs.

Pantoprazole was most commonly prescribed PPI in 82% of patients followed by omeprazole in 11% and esomeprazole in 7 % as shown in Table 10.

**Table 10:** Proton pump inhibitors used in the study

PPI	% of patients
Pantoprazole	82
Omeprazole	11
Esomeprazole	07

**Table 11:** Cost analysis of Proton pump inhibitors used in the study

Drug	Formulation	Dose	Freq uency	Cost per day
Pantoprazole	Oral	40 mg	OD	6.5 Rs
Pantoprazole	IV	40 mg	OD	60 RS
Omeprazole	Oral	20 mg	OD	3 RS
Esomeprazole	Oral	20 mg	OD	3 RS

OD= Once daily, RS=Rupees

Omeprazole and esomeprazole were cheaper in comparison to pantoprazole

**Table 12:** Common adverse effects during therapy with PPIs

S.No	Adverse effect	% of patients
1.	At least one adverse effect	14
2.	Headache	5
3.	Rash	3
4.	Abdominal pain	3
5.	Nausea	2
6.	Constipation	2
7.	Diarrhoea	1
8.	Rhinitis	1

## DISCUSSION

The prescriptions of proton pump inhibitors are increasing rapidly in India as well as worldwide and PPIs have become one of the most commonly prescribed drugs. The present study shows that total of 46.72 % of hospitalized patients were on proton pump inhibitors during the study period. This is in accordance with the previous study by Ramirez E et al<sup>28</sup>, who reported that the use of PPIs range from 28.65 % to 82.65% and Sandozi T<sup>17</sup> who reported use in 45 % of hospitalized patients. There was no significant difference in the prescription of proton pump inhibitor between the surgery and medicine departments ( $Z=0.442$ ). The use of PPIs was significantly more in males in comparison to females  $Z= 4.5081$ . This is in accordance with the previous study by Mayet AY<sup>16</sup>. Only 42 % of the patients were prescribed PPIs according to the criteria of rationality. 58 % of the prescriptions of PPI were unjustifiable. This is in accordance to the study by Sandozi T<sup>17</sup> (55 %) but more than the study by Mayet AY<sup>16</sup> (43%). Study by Brandhagen DJ et al<sup>29</sup> has reported 77.5% of unjustified prescriptions. Naunton M et al<sup>15</sup> (39.6%). The frequency of administration of PPIs was once daily in 97% of cases, the doses of PPIs are recommended as once daily but can be given twice daily also for rapid action as steady state is achieved rapidly. The most common concomitant medications used with PPIs were Antimicrobials, this is a serious issue as 58% of the prescriptions of PPI were unjustified and it is well known fact that patients on proton pump inhibitors are also susceptible to colonization of pathogens which can lead to bacterial gastroenteritis and also there is higher risk of development of infection by Clostridium difficile (antibiotic associated diarrhoea). 32% of cases PPIs

were given along with NSAIDS. This is in accordance with the studies by Kumar A et al<sup>30</sup> and Raghavendra B et al<sup>31</sup> who have found high incidence of co-prescription of PPIs with NSAIDs. The use of NSAIDs is an important predisposing factor for peptic ulcer disease in the community thus one of the important indications of PPIs is co-administration with NSAIDs to reduce the risk of gastrointestinal bleeding and peptic ulcers. In our study we used questionnaire based five point Likert assessment scale to evaluate the presence of GERD symptoms, dyspepsia and to assess the symptom severity and response to treatment.<sup>20</sup> Though a number of symptom scales and Quality of life instruments have been used in clinical trials, not all have been fully validated. We used the Reflux Disease Diagnostic Questionnaire (RDQ) as it is specific for GERD and dyspepsia. The validity, reliability and responsiveness of this test have been well demonstrated. In our study 47 % of patients had RDQ score of 12 indicating that majority of the patients had no symptoms of GERD as this was the minimum possible score and only 12% patients had significant symptoms as demonstrated by RDQ score of more than 20. There was significant improvement in the RDQ score of the patients demonstrating the efficacy of PPIs ( $Z= 3.86$ ). We cannot comment much on the efficacy as our study was non interventional and the duration of therapy with PPIs varied in the patients. The study design was not appropriate to evaluate our objective of efficacy with PPIs. Randomized prospective clinical trials are better in this regards. The most common proton pump inhibitor used was Pantoprazole in 82% of patients, followed by Omeprazole(11%) and Esomeprazole (7%). Atleast one adverse effect was seen in 14 % of the patients. Most common adverse effect was headache seen in 5 % of the patients. No serious or life threatening adverse effect was observed in patients receiving proton pump inhibitors. Cost analysis revealed that pantoprazole was twice more costly than omeprazole and esomeprazole formulations available in the hospital pharmacy.

## CONCLUSION

Fifty eight percent of the patients in our study received Proton pump inhibitors improperly for unjustified indications. Increased awareness should be created among the clinicians in the hospital so that appropriate prescription of PPIs will improve the patient care at

low cost. Although we found PPIs to be efficacious in our study, the study design was not suitable for evaluating efficacy. More drug utilization and pharmaco-economic studies should be conducted in future to compare the rationality of use of proton pump inhibitors and other anti secretory drugs like H2 blockers to know the exact scenario and plan the remedial measures.

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