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prestinthomas1991@gmail.com**A PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS THE INDICATIONS AND THE ADVERSE EVENTS OF PROTON PUMP INHIBITORS AMONG PATIENTS VISITING A TERTIARY CARE HOSPITAL IN COIMBATORE, INDIA****Prestin Thomas, Arulraj Ramakrishnan, A.Vijayakumar, G.Sathyaprabha and K.T.Manisenthilkumar****ABSTRACT**

The incidence of inappropriate use of proton pump inhibitors (PPIs) varies from 40-60% in various studies. The present study was planned with the aim of finding out the rational use of proton pump inhibitors (PPIs) in the patients of a tertiary care hospital. Prospective observational study of PPIs was conducted in Kovai Medical Center and Hospital for 5 months in the inpatients of Gastroenterology, General medicine and Neurology. The sample size of the study was 200. Rationality was determined by comparison with National Institute of Clinical Excellence (NICE) Guidance. Data of 200 inpatients were collected during the study period, in which 71.5% were males and 28.5% were females. It was observed that, of the Proton Pump Inhibitors used, Pantoprazole was utilized the most, constituting 66.5% of total prescriptions. When compared to the NICE guidelines, the study reveals that only 53% of the PPI's were prescribed for approved indications for GI disorders followed by 23% for prophylaxis of the same. For 24% (n=48) of patients, there was no documentation of valid indication for being on PPI. Since there is an increase in number of GI disturbances and hence the uses of PPI's, more studies are needed to ensure its use in those indications and to have a rational prescription of PPI. For a developing country like India, where the use of PPIs is increasing, it is high time to formulate a National Drug policy to rationalize drug use.

Key Words: Proton pump inhibitors, Rationale, NICE Guidance

INTRODUCTION

Acid-related disease involves a variety of disorders that can affect the esophagus, stomach and duodenum. In USA, approximately 2.3% of chronic acid-related disorders was found to be prevalent, with GERD constituting a greater proportion among them. Studies show that about 60 million American populations were affected with GERD compared to other acid related disorders. Peptic Ulcer Disease ranks second among the commonly occurring gastric acid disorders. This is generally triggered by the gastric acid; however this disease has an inverse association with the quality of life and increases the expense of patient care. However the scenario is different in India. Earlier studies done on GERD have shown a prevalence of 18-20% whereas one study states that there is a prevalence of 23.6% of GERD patients.¹ The introduction of PPIs marked a major therapeutic advance in the treatment of clinical problems due to excess acid secretion. Since the introduction in the late 1980s PPIs have demonstrated gastric acid suppression superior to that of histamine H₂ receptor blockers due to the potent and long-term suppression of acid release and superior efficacy in healing documented esophagitis.² PPIs are now among the most widely selling drugs worldwide due to their outstanding efficacy and safety and hence find use as a first line drug in the treatment of acid peptic disease.³

Proton pump inhibitors (PPIs) are class of drugs that act by suppressing the gastric acid production and thus maintain a low acid environment, thereby providing a relief to patients with acid – related disorders. They are the most potent drugs that are used clinically.⁴ These drugs irreversibly inhibit the gastric H⁺-K⁺ ATPase pump (proton pump) and decrease both basal and stimulated gastric output. Currently the

PPIs available in India are Esomeprazole, Pantoprazole, Omeprazole, Rabeprazole and Lansoprazole. PPIs are indicated therapeutically in active gastric ulcers, Gastro Esophageal Reflux Disease (GERD), Zollinger-Ellison syndrome, GI bleeding, NSAID induced gastritis and is used along with antibiotics for the treatment of *H.Pylori*.⁵ In patients with history of peptic ulcer / previous GI bleed / elderly patients PPIs are given prophylactically along with NSAID or Steroids.¹⁷ Because this drug finds solution to many medical problems.

In the year 2000, the National Institute for Health and Clinical Excellence (NICE) has published guidelines and recommended the PPI doses and duration in different clinical indications. Proton pump inhibitors have been found to be safe and effective drugs but in 5% of the patients prescribed with proton pump inhibitors short term adverse effects like headache, dizziness, diarrhea, fatigue, rashes and abdominal pain have been reported.^{6, 7} Long term use of PPIs have also been related with increased risk of hip fracture, and community acquired pneumonia.^{8, 9} In setting with low rate of such infections the benefits of PPI therapy outweighs the risk developing it. Such risks are valuable taking when concerned with those life saving drugs that are clearly indicated, but prescribing PPIs that may not be clinically necessary can put patients at risk of complications. Polypharmacy among elderly patients tends to confuse their use of medication schedule. Some reports suggest that upto 60% of patients suffering from dyspepsia are on drugs like PPIs without proper indication.^{10, 11} The incidence of inappropriate use of PPIs ranges from 40-70% in many studies.^{12, 13} Initiation and the prolonged use of these drugs without proper indications will result in significant cost and

risk to the patient hence, the present study is planned to know the rationale use of PPIs in the in patients of a tertiary care hospital.

Study Objectives

- To understand the present prescribing pattern of proton pump inhibitors in different departments.
- To review whether proton pump inhibitors are prescribed for appropriate indications.
- To identify the most commonly prescribed proton pump inhibitors.
- To find out the rationality of the prescription.
- Is there any report of Adverse Drug Reaction and Drug interactions?

MATERIALS AND METHODS

A prospective observational study was conducted in the inpatient wards of gastroenterology, general medicine and neurology in Kovai Medical Center and Hospital (KMCH), designed to assess the indications and adverse events of proton pump inhibitors. Two hundred patients who were taking PPI, from the month of March to July 2016 were included in the study. The study protocol was submitted to KMCH

ethics committee in the month of December 2015. Need for the study, study design, duration of study and sample size were presented to committee members. The committee has approved the study on 21-03-2016, KMCH Ethics Committee (Reg. No: ECR/ 112 / inst / TN / 2013). Based on the treatment employed, patients were classified into three groups namely 1.Approved indications 2.Prophylaxis 3.Unapproved indications.

Data was collected from clinical notes and recorded in a structured data collection form (appendix). The data collection form comprised of patient demographics, previous history of treatment, laboratory investigations, PPIs prescribed, dose and frequency, indications for its use and duration, any adverse drug reactions and also drug interaction. Adverse Drug Reactions was monitored by using Naranjo Adverse Drug Reaction Probability Scale. The data collected and the prescriptions were analyzed and reviewed. Rationality was determined by comparison with National Institute of Clinical Excellence (NICE) Guidance.²¹

RESULTS

Data of 200 inpatients were collected during the study period, in which 71.5% were males and 28.5% were females.

Table No.1. Gender wise Distribution among the Study Population(n=200)

Gender	No. of patients	Percentage
Male	143	71.5
Female	57	28.5
Total	200	100.0

The study showed that of all the PPIs prescribed; Pantoprazole was utilized the most, followed by Esomeprazole and Rabeprazole. Pantoprazole was most commonly prescribed PPI constituting 66.5%, followed by Esomeprazole constituting 32.5% and Rabeprazole 2 % of the total prescriptions.

Table No.2. Departments Prescribing PPIs among the Study Population (n=200)

Department Wise Distribution	No. of patients	Percentage
Gastroenterology	81	40.5
General Medicine	62	31.0
Neurology	57	28.5
Total	200	100.0

On categorizing the prescribed PPIs based on the department it was found that, the maximum number of PPIs is prescribed by the doctors in the department of gastroenterology with 40.5%, followed by the general medicine by 31% and thereafter by Neurology by 28.5%.

Table No.3. PPIs Prescribed among the Study Populations (n=200)

Choice of PPI	No. of patients	Percent
Pantoprazole	131	65.5
Esomeprazole	65	32.5
Rabeprazole	4	2.0
Total	200	100.0

The study showed that of all the PPIs prescribed; Pantoprazole was utilized the most, followed by Esomeprazole and Rabeprazole. Pantoprazole was most commonly prescribed PPI constituting 66.5%, followed by Esomeprazole constituting 32.5% and Rabeprazole 2 % of the total prescriptions. The frequency of administration of PPI was found to be once daily in 69.5% of cases and remaining 30.5% was given twice daily.

Table No.4. Frequency of PPI among study population (n=200)

Frequency	No. of patients	Percentage
Once daily	139	69.5
Twice daily	61	30.5
Total	200	100.0

There are several adverse effects reported with proton pump inhibitors. In the study population 11.5% of total patients prescribed with PPIs have shown adverse effects. Most common adverse effect reported was headache, which was found to be 4%. Other adverse effects such as constipation, abdominal pain, nausea and diarrhoea were also reported.

Table No.5. Adverse Drug Reactions of PPIs among Study Population (n=200)

Adverse Drug Reaction	No. of patients	Percentage
Doubtful	2	8.7
Possible	15	65.2
Probable	6	26.1
Total	23	100.0

Table No.6. Reason for Prescribing PPIs in the Study Population (n=200)

Indications		No of Patients	Percent	
Approved Indications	GERD	29	14.5	53
	Gastritis	32	16.0	
	Gastric Ulcer	13	6.5	
	Duodenal Ulcer	20	10.0	
	Esophageal Varices	9	4.5	
	H. Pylori	3	1.5	
Prophylaxis	NSAIDs	21	10.5	23
	Anti-platelets	15	7.5	
	Anti-platelets + Anti-coagulants	10	5.0	
Unapproved	Anti-coagulants	5	2.5	24
	Steroids	11	5.5	
	Anti-epileptics	6	3.0	
	Antibiotics	16	8.0	
	Others	10	5.0	
Total		200	100.0	

The results showed that among 53% of the total population, the PPI's were prescribed for approved Indications. 23% of the patients, who were at greatest risk for serious GI complications, received PPIs as prophylactic treatment. Whereas 24% of the PPIs prescribed has no definite indication.

DISCUSSION

Proton Pump Inhibitors are widely prescribed for Acid- Peptic disease. In general, the safety of this class of drugs has been excellent. All over the world the

prescriptions of Proton Pump Inhibitors are increasing day by day. In the present study on the use of PPI in inpatients at a Super Specialty hospital (200 inpatients) it was

found that 71.5% were males and 28.5% were females indicated for use of PPI. The result obtained from this study was in accordance with the results of the previous study which had reported that 61% of study populations were males and 39% were female patients¹⁴. In another study reports shows that the use of Proton Pump Inhibitors was more significant among males (57.9%) as compared to females¹⁵.

The result showed that 62.5% of the total populations were over the age of 50 years. People over the age of 50 years were at an increased risk for gastrointestinal complications associated with age related changes in gastric mucosal defense. This is in accordance with the previous study which reported that the mean age group of the patients who were taking Proton Pump Inhibitors was 61 ± 14.27 . When the percentage of PPI prescriptions were categorized according to the departments, it was seen that 40.5% of the PPIs were prescribed by gastroenterology, 31% by general medicine and remaining 28.5% by neurology¹⁶.

It was observed that, of the Proton Pump Inhibitor used Pantoprazole was utilized the most constituting 66.5%, followed by Esomeprazole (32.5%). In contrast to previous study which quotes that Esomeprazole was prescribed for 38% and Pantoprazole was accounted for 34% of overall prescriptions¹⁶. The frequency of administration of PPI was found to be once daily in 69.5% of cases. Even though the frequency of PPI's were recommended once daily, it can also be given twice daily for rapid action, as steady state is achieved rapidly. This result was again found to be in accordance with the previous study by Nousheen *et al.*, which reports that majority of patients were prescribed with PPI's once daily (97%) and only in 3% of patients, twice

daily therapy was administered. Oral therapies with PPI's were prescribed in 43% of patients and intravenous PPI's in 57% of the patients. 98% of the total population received 40 mg as the recommended dose and 2% of the population received 20 mg as the recommended dose. Rabeprazole was the only drug which was prescribed at the strength of 20 mg in this study.

The results showed that among 53% of the total population, the PPI's were prescribed for approved indications, which was found to be similar with the results of the previous study conducted by Christopher Tze Wei Chia *et al*¹⁷ and Nousheen *et al*¹⁴ which reported 45.9% and 42% of approved indications respectively. 23% of the patients who were at greatest risk for serious GI complications received prophylactic treatment. 24% of the prescriptions were given for the conditions in which the use of PPI is not indicated. This was found to be in accordance with the previous study by Nousheen *et al*¹⁴ which showed that there were 58% non-indicated prescriptions. Another study by Mayet AY *et al*¹⁵ showed 43% non-indicated prescriptions. This study showed that only 53 % of the PPI's prescribed were for approved indications when compared with NICE guidance.

Ulcers have been reported with low doses of aspirin or non-aspirin NSAIDs and complications have occurred following a few days of treatment. Patients who are taking concurrent high doses of NSAIDs or antiplatelets are at the greatest risk for serious GI complications. PPI co-therapy has been shown to lower the incidence of dyspepsia in those taking NSAIDs. So this study favours the use of PPIs for reducing the risk of GI complications. This study resembles the studies by Muhammad Haroon *et al*¹⁶ and Kumar A *et al*⁴² where 20% and 21.65% of the total cases were PPIs were

prescribed along with NSAIDs. The study showed that 11 % of the PPIs were prescribed along with antibiotics, in order to prevent the gastritis occurring with antibiotics. However no literature was available to support the need for prescribing PPIs along with antibiotics.

In general Proton Pump Inhibitors (PPIs) are well tolerated and the incidences of short term adverse effects were relatively low. The extend of occurrence of adverse effects are similar for all of the PPI's though they have been reported more frequently with Omeprazole. At least one adverse effect was reported in 11.5% of the patients. Most common adverse effect reported was headache and constipation. No serious or life threatening adverse effects were observed in patients receiving proton pump inhibitors. The Naranjo algorithm is a questionnaire designed by Naranjo *et al.*,¹⁸ for determining

the likelihood of whether an ADR is actually duo to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible, or doubtful. In this study 7.5 % of the total study population shows possible Adverse Drug Reaction according to Naranjo algorithm scale.

The study conducted by Yu-Xiao Yang *et al*¹⁹ suggested that that use of PPIs could induce Calcium mal-absorption and lead to osteoporosis with a subsequent risk of fracture, especially hip fracture and was significantly greater in patients who had been using PPI's for at least one year. Mei-Ling Blank²⁰ have evaluated the association between PPI use and Acquired Interstitial Nephritis, while other studies have evaluated the relation between PPI use and the chance of Community Acquired Pneumonia, *Clostridium difficile* infection.

CONCLUSION

The results of the present study reveals that 24% of the patients received Proton pump inhibitors without proper indications. For a developing country like India, where the use of PPIs is increasing, it is high time to formulate a National Drug policy to rationalize drug use. An Institutional Guidelines for prescribing PPIs could be designed collaboratively by Gastroenterologists, other physicians and pharmacists to rationalize the use of PPIs. Increased awareness should be created among the medical practitioners in the hospital so that PPIs with appropriate prescriptions will improve the patient care at low cost. With an increase in number of GI disturbances and the use of PPI, more studies are needed to ensure the use of PPI in those

indications and to have a rational prescription of proton pump inhibitors.

Conflict of interest

Authors declare no conflict of interest.

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