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RESEARCH ARTICLE

An observational study on adverse drug reaction profile in patients on long-term treatment with proton pump inhibitors

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ABSTRACT

Background: Proton pump inhibitors (PPI) are most commonly prescribed medications in the world which are highly effective drugs in treatment of upper gastrointestinal disorders, but there are concerns regarding its long term use. **Aim and Objective:** To assess the pattern of reported adverse drug reactions (ADR) in patients with long term use of PPI and to estimate the frequency of adverse drug effects**. Materials and Methods:** A study conducted as an observational study among 100 consecutive patients who attended the medical-gastro inpatient and outpatient department on treatment with PPI for more than 4 months, according to inclusion and exclusion criteria. After attaining the written informed consent, data regarding patient's demographic details, occupational status, addictions, co-morbidities, and lab investigations were recorded in pre-prepared proforma after interviewing the patient and referring the case sheet. Details including PPI used and per day dose of the drug with any ADR developed were noted. Data collected were analyzed using appropriate statistical method. Categorical variables are expressed as frequency (percentage) and continuous variables as mean (standard deviation). Chi-square test was used to find out the association between PPI and ADR. **Results:** Out of 100 study participants, 57% case reported ADR which included 19 cases (33.3%) of hypomagnesemia, 8 cases (14%) each of hypocalcemia, and hyperkalemia, 7 cases (12.3%) of anemia, and 5 cases (8.9%) of acute kidney injury. Out of the 57 reported adverse events, 29 (50.9%) were caused by Rabeprazole followed by 18 (31.6%) by Pantoprazole, then Esomeprazole: 8 (14%), and least by Omeprazole (3.5%). **Conclusion:** Long-term use of PPI can lead to various ADR which requires the withdrawal of drug. Since PPIs are easily available without prescriptions, self-medication with PPIs are increasing alarmingly. With every antibiotic one PPI is always prescribed, as a result, there is irrational use of PPIs which is of concern and requires attention. These adverse events could be reduced by preventing self-medication of long duration and reducing the irrational prescribing of PPIs. Doctors should be sensitized about the ADRs. The patient should be educated about the long-term adverse effects of PPIs.

KEY WORDS: Proton Pump Inhibitors; Long-Term Use; Adverse Drug Reaction

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INTRODUCTION

Proton pump inhibitors (PPI) are one of the most commonly prescribed medications all over the world and are highly effective drugs in treatment of upper gastrointestinal disorders including symptomatic gastroesophageal reflux disease (GERD), erosive esophagitis, NSAIDs induced gastric ulcers

and hypersecretory conditions (Zollinger-Ellison Syndrome) and dyspepsia.[1] Long term, sometimes lifelong use is becoming increasingly common.[1] From pharmacokinetic perspective PPIs are ideal drugs.[2] Pantoprazole, Rabeprazole, Omeprazole, Esomeprazole, Lansoprazole, and Dexlansoprazole are the available PPIs. They are easily available and over the counter tablet.

Long-term PPI therapy varies from one repeated prescription over 12 months to continuous therapy for periods ranging from four to more than 12 months.[3] The most of the time PPIs are given along with other agents such as antibiotics or analgesics. When these drugs are taken for a longer time, PPIs are also taken along with it. PPIs are the most successful class of drugs that have been introduced because of their profound and consistent effect on gastric acid secretion.

They have demonstrated an excellent adverse effect profile after many years of clinical use. Healing rates in erosive esophagitis is achieved more than 90%. Complete symptom resolution is achievable in patients with Barrett's esophagus. Complications of these conditions, such as esophageal stricture, ulceration and others, are becoming less frequent because of PPI treatment.

Despite the acceptable safety, there are concerns regarding its long-term use. Many adverse effects are reported

Table 1: Distribution of age group

Age (in years)	Frequency (*n*)	Percent (%)
18–40	41	41
41–60	49	49
>60	10	10
Total	100	100

Table 2: Distribution of gender

Gender	Frequency (*n*)	Percent (%)
Female	44	44
Male	56	56
Total	100	100

Table 3: Distribution of participants bases on duration of PPI therapy

Duration (months)	Frequency	Percent
<25	90	90
25–50	5	5
>50	5	5
Total	100	100

Table 4: Distribution of ADRs with PPI used

PPI Used	Adverse events reported	Frequency
Rabeprazole	29	50.9
Pantoprazole	18	31.6
Esomeprazole	8	14
Omeprazole	2	3.5
Total	57	100

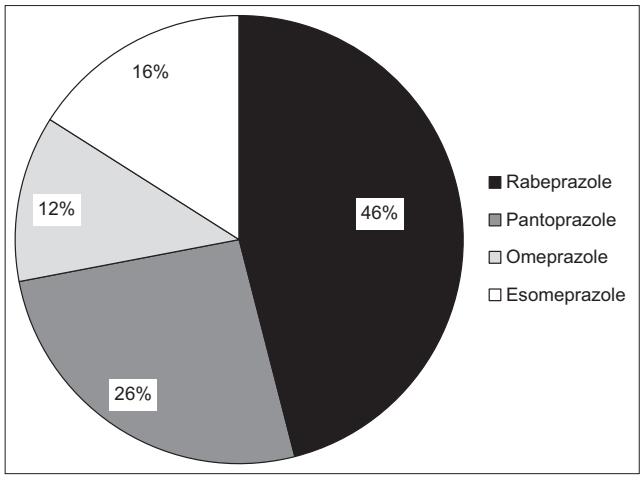

Figure 1: Distribution of proton pump inhibitors used

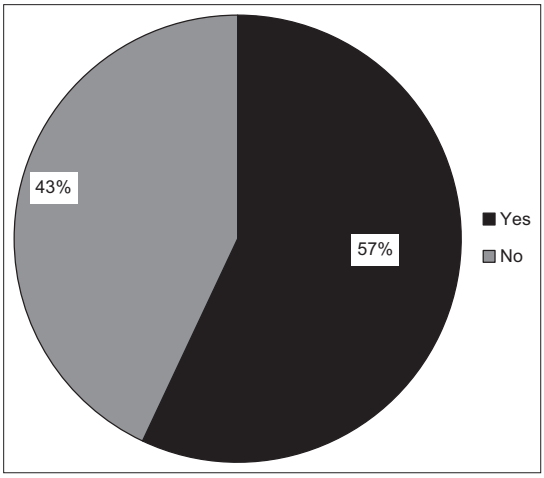

Figure 2: No. of patients who reported adverse events with proton pump inhibitors and no of patients who did not report any adverse events

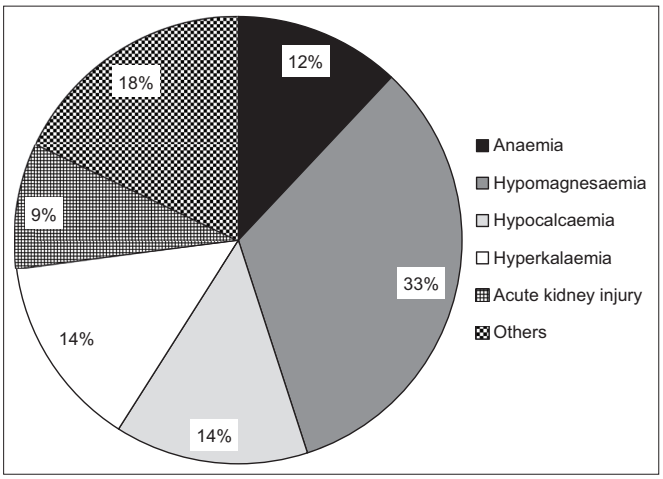

Figure 3: Distribution of participants with reported adverse events

because of their widespread use that recently has received little attention.

MATERIALS AND METHODS

It is an observational study conducted in patients attending the Gastromedicine inpatient and outpatient department of a tertiary care center in Kerala who were on PPI for more than 4 months. With an assumed proportion of 0.27 and acceptable difference of 0.09 with confidence interval of 95%, required sample size is 94, which was rounded up to 100. Both male and female patients who were more than 18 years of age on PPIs for more than 4 months were included in the study. Pregnant and lactating females and those who were not willing to give informed written consent were excluded.

Approval from the institutional ethics and research committee and consent from the study participant were obtained. Data regarding patient demographic details and clinical information were collected from case sheet or by interviewing the patient using a pre-prepared proforma. Adverse drug reactions (ADR) were based on patient's complaints and lab investigations. A study provided the prevalence of various ADR associated with long term use of PPI. Data were entered in Microsoft Excel and analyzed using appropriate software. Qualitative variables were expressed as percentages and quantitative variables as mean and standard deviation**.** Chi-square test was used to find out the association between PPI and ADR.

RESULTS

Out of 100 study subjects, maximum participants belonged to age group of 41–60 years 49 (49%), followed by 18–40 age group and then >60 years age group [Table 1]. Mean age in the study subject was 43.35 years. Out of 100 study participants, 44 (44%) were females and 56 (56%) were males [Table 2]. The majority of the participants belonged to teaching profession (36%) followed by students and unemployed (both 14%) and then IT professionals (10%). Out of 100 study participants, the majority of them (76%) do not have any addictions. Moreover, out of those patients with addictions majority of them were chronic smokers.

The majority of participants belonged to the group of <25 months of treatment (90%) followed by 25–50 months group and >50 months of treatment (5%) [Table 3]. Mean duration of treatment is 15.590. The main indication for proton pump therapy was gastritis and dyspepsia which was seen in 37% cases each. 20% cases were having GERD followed by 5% cases of esophagitis. Only one case came with NSAIDs induced gastritis [Figure 1].

Out of 57 reported adverse events, 19 cases were hypomagnesemia (33.3%). 8 cases each of hypocalcemia and hyperkalemia were reported (14% each). 7 cases (12.3% Other 10 cases that were reported 5 cases were gastrointestinal polyps, 3 cases of elevated liver enzymes and 2 cases of hyponatremia [Figures 2 and 3]. Out of the 57 reported adverse events, 29 (50.9%) were caused by Rabeprazole followed by 18 (31.6%) by Pantoprazole, then Esomeprazole: 8 (14%), and least by Omeprazole (3.5%) [Table 4].

DISCUSSION

The study design was an observational study which included 100 study participants who fulfilled inclusion and exclusion criteria. The study group included 56 males and 44 females. All the study participants were of age >18 years who are on PPIs for more than 4 months. Maximum patients belonged to age group of 41–60 years followed by 18–40 age group and then >60 years of age group. Mean age was 43.5 years. the majority of participants belonged to the group of <25 months of treatment group. PPIs prescribed in Gastromedicine department were Rabeprazole, Pantoprazole, Esomeprazole, and Omeprazole. Among the study participants 46% of them were on Rabeprazole followed by Pantoprazole (26%), 16% on Esomeprazole followed by Omeprazole (12%). 36 % cases belonged to teaching profession followed by students and IT professionals and also seem in unemployed people. The majority (76%) of participants did not have any addictions. Those participants with addictions, most of them were chronic smokers. The main indication for starting proton pump therapy in these participants were gastritis and dyspepsia which was seen in 37% of cases followed by GERD which was seen in 20% cases followed by 5% cases of esophagitis.

Out of 100 study participants, 57% cases reported ADR whereas 43% patients did not report any ADRs. Out of 57 reported adverse events, 19 cases (33.3%) were hypomagnesemia. Chrysant in his study discussed that PPIs cause hypomagnesemia, which could be associated with serious cardiac arrhythmias including torsades de pointes. However, its incidence is not very common as many people take PPIs. FDA has advised to be monitor this serious adverse effect of PPIs and check the magnesium levels before initiation of PPI treatment.[4] In the present study, hypocalcemia and hyperkalemia were the other adverse events reported. 8 cases each of hypocalcemia and hyperkalemia were reported (14% each). Gau *et al*. showed in his study that higher serum potassium levels were observed among PPI users when compared to PPI non-users. Gau *et al*. also found out high daily dose PPI therapy may be an independent positive predictor of serum potassium levels.[5] In our study, 7 cases (12.3%) of anemia were reported. Sarzynski *et al*. in his study showed that all hematologic indices decreased from baseline, including hemoglobin, hematocrit and mean corpuscular volume (27). Sharma *et al*. in his study found out that Omeprazole and possibly all PPI decrease the absorption of oral iron supplementation. Iron-deficient patients taking

PPI may have to be treated with high dose iron therapy for a longer duration or with intravenous iron therapy.[6] In our study, other 10 cases that were reported 5 of them were gastrointestinal polyps, 3 cases of elevated liver enzymes, and 2 cases of hyponatremia. Mcloughlin *et al*. in his study showed that long-term PPI therapy may be associated with benign fundic polyps, but these are considered rare and reversible on stopping therapy.[3] The present study reported 8.9% cases (5 cases) of acute kidney injury. Avinash *et al*. conducted a study where PPIs were administered for at least seven consecutive days and blood urea and creatinine were noted. His study that renal injury was more common in the age group of over 50 years of age. Pantoprazole was the most common drug involved. It is important to check patient's renal profile so as to avoid any decline in renal function.[7]

Due to small sample size and shorter duration of the study, only a few side effects could be studied, as the patients were not followed up any improvement in the adverse reactions could not be evaluated.

CONCLUSION

The observations and results from the study suggest that long-term use of PPI can lead to various ADR which requires the withdrawal of drug. Since PPIs are easily available without prescriptions, self-medication with PPIs is increasing alarmingly. With every antibiotic one PPI is always prescribed, as a result there is irrational use of PPIs which is of concern and requires attention. These adverse events could be reduced by preventing self-medication of long duration and reducing the irrational prescribing of PPIs. Doctors should be sensitized about the ADRs. Patient should be educated about the long term adverse effects of PPIs.

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