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ORIGINAL ARTICLE

A Study of Empirical Use of Proton Pump Inhibitors in Indoor Patients

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ABSTRACT

Background: Proton pump inhibitors are amongst most widely used gastric protectants due to their effectiveness. However, there are concerns about their over utilization, patient safety and socioeconomic burden.
Aim: To evaluate empirical use, risks and hazards associated with over- usage of Proton pump inhibitors (PPIs).
Methodology: A descriptive cross-sectional study was conducted at a tertiary care hospital in Lahore from July to August 2021. Seventy five patients were randomly picked up from indoor wards of the hospital. Patient's demographic data and frequency of PPIs usage was recorded. Route of administration, adverse effects and indications of proton pump inhibitors were also noted in percentages.
Results: All patients were prescribed PPIs on their admission day. Among them, two patients were concomitantly taking H_2 Receptor Blockers. Seventy eight (78 %) users were administered PPIs through intravenous route, while rest were given once daily oral formulation. Fourty two (42) % of patients were not prescribed PPIs according to AGA criteria. Moreover, 12% of our sample population suffered from different adverse effects like diarrhea, abdominal pain, bone pain and headache. The results of our study clearly indicated frequent use of PPIs in indoor patients as a prophylaxis of SRMD.
Conclusion: Keeping in view the incorrect use of antiacids and their adverse effects including increased risk of enteric and hospital acquired infection, unnecessary use of PPIs in admitted patients should be monitored regularly.
MeSH words: PPIs, SRMD, NSAIDs, AG

INTRODUCTION

It has been a general perception among the clinicians that the stress component of chronic diseases and use of NSAIDS do inevitably lead to development of acid peptic disease (APD). Gastrointestinal ulcer and subsequent complications like GI bleeding, perforation and obstruction are the basic reasons to treat stress related ulcer disease. This ailment needs to be treated even before the clinical signs of stress related or NSAIDS-induced mucosal damage are actually developed[1-2].

Drugs being used for this pre-emptive therapy are Proton Pump Inhibitors (PPIs) which can literally bring the HCl production to zero and H2 receptor blockers[3]. Prostaglandin E 1 analogue (misoprostol) has also been implicated for prevention of NSAID induced gastric ulcer though their use has been limited due to multiple daily dosing and severe adverse effects like diarrhea and GIT upset[4].

There are growing evidence regarding PPIs effectiveness in treatment of stress related mucosal damage. These drugs first undergo activation and then act by irreversible inhibition of H^+/K^+ ATPase pump in gastric parietal cells. PPIs possess longer duration of action owing to their direct effect on site of action although their plasma half life is short[5]. Pharmacokinetic studies reveal that maximal inhibition of proton pumps can be achieved by continuous intravenous administration of esomeprazole and pantoprazole rather than single IV injection[6].
PPIs have been indicated for the treatment of peptic ulcer, stress related mucosal damage, esophagitis and gastro esophageal reflux disease (GERD). Although PPIs are considered as safe drugs, numerous studies proposed their long-term adverse effects including Vit B12 deficiency, anemia, osteoporosis, hypergastrinemia, spontaneous bacterial peritonitis and clostridium difficile infections in cirrhotic patients. These side effects are generally overlooked by the prescribing physicians. Inappropriate use of PPIs can also lead to drug-drug interactions and increased cost of hospital stay[7].

Overutilization of PPIs has been observed since late 1980s. These are among the most widely selling drugs due to their easy accessibility and emergence of new generics. According to a report by Brown T in 2015, expenditures of esomeprazole are estimated to be $6.1 billion annually[8]. However, limited local studies have been carried out regarding frequency of PPIs use in hospital settings. Hence we designed the current study to estimate about frequency of inappropriate indications and hazards associated with PPIs administration in indoor patients.

The objectives of the study were to determine the frequency of empirical use of proton pump inhibitors and review the risks and hazards associated with such overuse of proton pump inhibitors.

METHODOLOGY

This cross-sectional study was carried out at 500 bed Tertiary Care hospital in Lahore after approval from institutional review board of the hospital. All the performed experiments were in accordance with latest version of Helsinki Declaration.

A total of seventy-five (75) patients were picked up randomly from different indoor wards of the hospital. An informed consent from all participants was taken prior to initiation of research project. Adult patients taking PPIs were included in the study. Method by Hoteit et al., 2015 was adopted with minor changes[9].

Patient's age was calculated as Mean± standard deviation, while gender was described in percentages. Appropriate use of PPIs was noted as per American gastroenterology association (AGA) guidelines. Patients having comorbidities like acid peptic disease, chronic liver disease, sepsis and coagulopathy were also determined in percentages. Frequency of NSAIDS and corticosteroids users was also noted[9]. Data was collected and analyzed in a tabular form using Microsoft Excel and SPSS version 20.

RESULTS

We included seventy-five adult patients in our study. Mean age was calculated to be 50.43 ± 3.2 years. Gender was described in percentages, 69.3% of our study population was male while 30.6% of patients were females (Fig 1, Table 1). All patients were prescribed PPIs on their admission day. Sixty patients were getting injectable (78.6%) while 15 subjects were getting oral PPIs (21.3%) with once daily dosing. Four patients (5.2%) developed severe abdominal discomfort after having first dose and further administration of PPIs to them was stopped (Fig. 2, Table 1).

According to our study, out of 75 patients taking PPIs, only 13 (17.3%) had a history of APD while only one patient was

investigated for presence of Helicobacter pylori. Only ten patients (13.3%) using PPIs were labeled cases of chronic liver disease / cirrhosis. Two patients (2.7%) were post operative surgical patients. Patients suffering from coagulopathy and sepsis were found to be (5.3% and 2.8%) respectively. Only seven patients were using NSAIDS (9.3%) and two patient was having oral Corticosteroids (2.6%). None of these patients had any signs or history of APD.

Fig 1: showing gender distribution of patients.

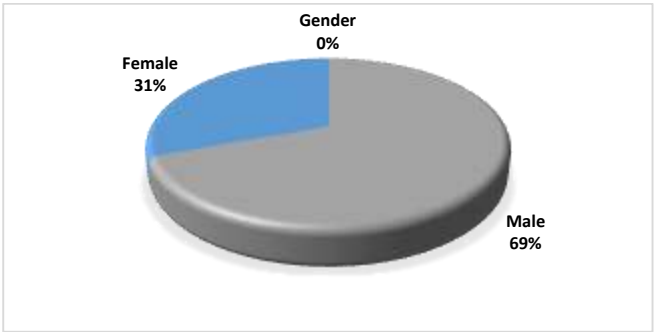

Fig 2: Graphical representation of adverse effects of PPIs

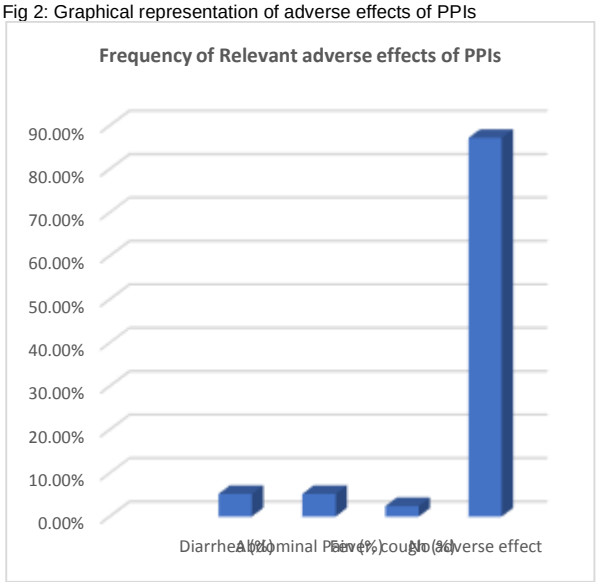

Fig 3: Graphical representation of indications for PPIs usage

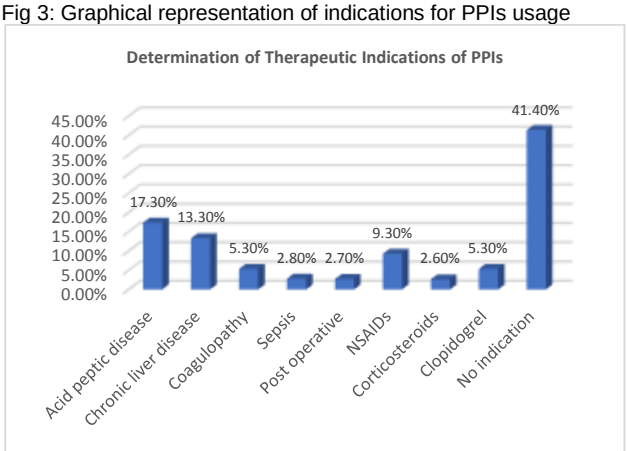

Table 1: Characteristics of PPIs users (n= 150)

Variables	**Percentage**		
Age (years) Mean ± S.D	50.43± 3.2		
Gender	**Male**	**Female**	
	69.3%	30.6%	
PPIs Routes of administration	**Oral**	**Intravenous**	
	21.3%	78.6%	
Relevant adverse effects of PPIs	**Diarrhoea**	**Abdominal pain**	**Fever, couth**
	5.2%	5.2%	2.4%

Table 2: Determination of Appropriate Indications for PPIs (n=150)

Frequency of associated diseases (percentage)	
Acid peptic disease	17.3%
Chronic liver disease	13.3%
Coagulopathy	5.3%
Sepsis	2.8%
Post operative	2.7%
Frequency of prescribed drugs (percentage)	
NSAIDs	9.3%
Corticosteroids	2.6%
Clopidogrel	5.3%

DISCUSSION

There is high prevalence of incorrect use of anti-acid drugs in hospitalized patients[10]. These medications have also been frequently prescribed to patients discharged from hospital[11]. PPIs safe usage has been justified in critically ill patients but these drugs should only be used as an alternative to H2 receptor antagonists/sucralfate/prostaglandins since preference of PPIs over these agents has not been well documented for preventing Stress Related Mucosal Disease (SRMD)[12].

Numerous research studies have been conducted on inappropriate use of PPIs but small sample size and lack of blinding remained major drawbacks of these studies[13]. Moreover, PPIs superiority for control of rate of bleeding from stress ulceration over placebo has not been established yet[14].

The results of our study clearly indicate that proton pump inhibitors are frequently being used in indoor patients as a prophylaxis for SRMD. Among them only 58.6% patients were appropriately indicated PPIs as per AGA guidelines and 41.4% patients were taking PPIs without any justified indication. This finding is in accordance with a local study conducted by Samar et al, 2021 at Agha Khan Hospital where 66% patients had been frequently prescribed PPIs without any indication[15].

In our study, 13.3% cirrhotic/CLD patients were prescribed oral PPIs along with other drugs. The majority of cirrhotic patients have hypochlorhydia and gastric pH of liver cirrhosis patients is higher than that of control[16]. Acid secretion is constitutively decreased during cirrhosis, so there is no evidence about prophylactic use of PPIs in patients with portal hypertension or esophageal varices complications[17].

We found that 21.3% subjects were prescribed oral PPIs (omeprazole 40mg once daily) while 78.6% patients had been administered injectable omeprazole once or twice daily at same dose. Hoteit et al., 2020 presented similar findings where more than 40% of PPIs users were given the drug by oral route in tertiary care hospital of Lebanon[9]. Change in route of administration can result in effective management of these patients. Literature suggests that intermittent dosing with an intravenous proton pump inhibitor may be an alternative to oral PPIs and high dose continuous infusion of a H2 receptor antagonist in critically ill patients[18].

PPIs are known to have a rapid first pass metabolism and systemic hepatic metabolism. They inactivate the gastric proton pump irreversibly for 24 hours. At least 18 hours are required for synthesis of new H^+/K^+ ATPase pump molecules. Because not all pumps are inactivated with the first dose of medication, up to 3-4 days of daily medication are required before the full acid inhibiting potential is reached. Similarly, after stopping the drug, it takes 3-4 days for full acid secretion to return[19].

Although inhibitory effect of PPIs on acid secretion improves its own relative bioavailability by decreasing acid secretion, PPIs adverse effects like headache, diarrhea, rashes, dizziness, somnolence, mental confusion, impotence, gynecomastia and pains in muscle and joints have been frequently reported[7].

Current study shows various associated side effects with long term administration of PPIs in indoor patients. We found that 5.2% of patients were suffering from diarrhea and abdominal pain while 2.4 % of patients had symptoms of pneumonia and were being treated accordingly.

Harmful effects of chronic PPI therapy include hypergastrinemia, ECL hyperplasia and parietal cell hypertrophy leading to rebound acid hypersecretion[20]. Jianu *et al* 2012 described first case of ECL cell derived neuroendocrine carcinoma due to hypergastrinemia secondary to PPI use for more than a decade [21]. These adverse effects may require close monitoring and surveillance throughout the hospital stay.

Since gastric acid play an important role in prevention of bacterial colonization and infection of the stomach and intestine, hypochlorhydria due to any reason increases the risk of enteric infections (eg Shigella, Salmonella). Several studies support hospital acquired Clostridium difficle associated diarrhea (CDAD) and community acquired pneumonia (CAP) with PPI usage [22]. To avoid these side effects, appropriate use of PPIs for shorter duration of time should be adopted by prescribing physicians.

CONCLUSION

It has been concluded that despite being safer drugs, PPIs are being overprescribed in indoor & outpatient clinics. Keeping in view the pharmacokinetics of Proton Pump Inhibitors, it may be suggested that instead of their continuous use, these drugs should be given intermittently, if necessary. In hospitalized patients, the preferred route of administration (keeping the cost factor in view) should be intravenous as the bioavailability after continuous oral administration cannot be anticipated exactly. The benefits of use of PPIs in the patients with the advanced chronic liver disease should be gauged against potential hazard of exacerbating the hypochlorhydria that might already be present in such patients.
Additional comparative studies with adequate patient numbers and pharmacoeconomic analyses are needed before PPIs are considered as agent of choice for stress ulcer prophylaxis.

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