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A prospective study on prescription pattern of proton pump inhibitors in gastrointestinal disorders

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Abstract
Background: Proton pump inhibitors (PPIs) are widely prescribed classes of medications that are used in the treatment of multiple gastrointestinal (GI) disorders like 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) infections.
Methodology: A Prospective observational study was conducted in 190 patients. Pertinent information was collected from patients and prescribing pattern of PPIs was analyzed among the gastrointestinal disorders.
Results: Of 190 patients with gastrointestinal disorders, male patients were 59% and these disorders were observed more in the age group of 41-50 years (26%). Among 190 patients, the most commonly observed gastrointestinal disorders were gastric ulcer (29%) followed by gastritis (23%). In this study, PPIs were frequently prescribed as monotherapy (84%) and the most commonly prescribed PPI was pantoprazole (48%) followed by rabeprazole (34%) and esomeprazole (18%). In *H*. pyloric infections most commonly used *H*. pyloric kits were esomeprazole kit (54%) followed by pantoprazole kit (46%).
Conclusion: We observed that the most commonly observed gastric disorders were gastric ulcer and gastritis and the most commonly prescribed PPIs were patoprazole followed by rabeprazole. *H*.pyrolic infection was treated more with esomeprazole kits. The usage of pantoprazole was more as it was the most preferred drug in the majority of the gastric disorders observed and also it is one of the recommended drugs by NLEM.

Keywords: Gastric disorders, PPIs, peptic ulcer disease, prescribing pattern

Introduction
Proton pump inhibitors (PPIs) are widely prescribed class of medications that are used in the treatment of multiple gastrointestinal (GI) disorders like 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 exert their effect by inhibiting the H+/K+-adenosine triphosphatase (ATPase), or proton pump, which is located in the highly acidic lumen of parietal cells. This highly acidic environment enables the PPI to become protonated to its active metabolite which then irreversibly inhibits the activity of the proton pump, resulting in an increase of gastric pH. This class of medications has revolutionized the way in which clinicians manage acid-related disorders of the GI tract [2].
H2 -receptor antagonists are limited in their ability to inhibit postprandial gastric acid secretion and are ineffective in controlling reflux symptoms and healing esophagitis. In contrast to H2 receptor antagonists (H2RAs), proton pump inhibitors block the final step of acid secretion, resulting in a profound and long-lasting acid suppression regardless of the stimulus [3].
Proton pump inhibitors (PPIs) like Omeprazole, Lansoprazole and Pantoprazole, produce profound gastric acid suppression, and are the most effective treatment for gastro –esophageal reflux disease. They are effective short term treatments for gastric and duodenal ulcers. They may achieve a faster healing rate than H2 -receptor antagonists, but the relapse rate is similar. PPIs are also used in combination with antibacterial for Helicobacter pylori eradication. PPIs are generally well tolerated [4]

FDA approved indications of PPIs

Table 1: FDA-approved indications of the Proton Pump Inhibitors

Indication	Esomeprazole (Nexium™)	Lansoprazole (Prevacid®)	Omeprazole (Prilosec™)	Pantoprazole (Protonix®)	Rabeprazole (Aciphex™)
Healing of erosive esophagitis	X	X	X	X	X
Maintenance of healed erosive esophagitis	X	X	X	X	X
Symptomatic gastroesophageal reflux disease	X	X	X	X	
Eradication of *Heliobacter pylori* infection	X	X	X		
Prevention of NSAID-induced gastric ulcers		X			
Treatment of NSAID-induced gastric ulcers		X			
Healing of gastric ulcer		X	X		
Healing of duodenal ulcer		X	X		X
Maintenance of duodenal ulcer		X			
Treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison Syndrome)		X	X		X

PPIs like esomeprazole, lansoprazole, pantoprazole, omeprazole and rabeprazole are foung to be effective in healing of erosive esophagitis and maintenance of healed erosive esophagitis. Among the PPIs lansoprazole is indicated in almost all the gastric disorders mentioned in table 1.

Pharmacokinetic parameters of various PPIs

Among the PPIs, the highest bioavailability is observed in esomeprazole (90%) followed by lansoprazole (80%) and the least bioavailability is observed in omeprazole (30-40%). Protein binding is almost same in all PPIs. Among the PPIs, there is only slight variation in half life's of various PPIs [5].

Table 2: Comparison of the Pharmacokinetic Parameters of Various PPIs

Parameter	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Bioavailablitiy	90%	80%	30-40%	77%	52%
Acid liable	Yes	Yes	Yes	Yes	Yes
Enteric-coated formulation	Yes	Yes	Yes	Yes	Yes
Time to peak	1.5 hours	1.7 hours	0.5-3.5 hours	2.5 hours	2-5 hours
Half-life	1.2-1.5 hours	< 2 hours	0.5-1 hour	-1.9 hours	1-2 hours
Excreted unchanged in the urine	< 1%	< 1%	0%	0%	0%
Cytochrome P450 pathway*	CYP2C19, CYP3A4	CYP3A, CYP2C19	CYP2C9, CYP2C8, CYP2C18, CYP2C19, CYPA3/4, CYP3A1A2	CYP2C19, CYP3A4	CYP3A, CYP2C19
Protein binding	97%	97%	95%	98%	96.3%

Even though, PPIs are considered to be very safe drugs, they are not completely devoid of problems or potential problems. Some well-known adverse effects of long term administration of PPIs are rebound hypergastrinemia, greater incidence of community acquired pneumonias, vitamin B12 deficiency and enhanced risk of hip fractures especially older women. There are significant risks of drug interactions with a number of drug groups, notable amongst them are ketoconazole, ampicillin, iron, digoxin, theophylline, warfarin, diazepam, atazanavir and phenytoin [6].

Proton pump inhibitors (PPIs) are a major economic burden for the healthcare system in many countries. Concerns have been raised about the increasing costs associated with prescription of these drugs as they are often prescribed for minor symptoms and without clear indications. Studies from US, Australia and Europe have demonstrated overuse of PPIs in hospitalized patients and in primary care [7].

Several factors might influence the prescribing patterns of PPIs. It has been demonstrated that patient related factors have some impact on 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 [1].

Methodology

A prospective observational study was conducted in a gastroenterology clinic in Warangal region over a period of 3 months. 190 patients with gastro intestinal disorders were collected. A pre-designed and pre-tested proforma was used to collect the required information.

Inclusion criteria: Gastro intestinal disorders with PPI therapy in patients of age 10-80 years were included.

Exclusion criteria: Out patients without PPIs in their treatment regimen and in-patients were excluded

Results

Among the study population, gastrointestinal disorders were mostly observed in of 41-50 years age group (26%). Male were more affected than female with 59% and 41% respectively. In the present study mono therapeutic use of PPIs (84%) was preferred over combination therapy (PPIs & domperidone) (16%). The most commonly observed gastrointestinal disorders were gastric and duodenal ulcers (29%) followed by gastritis (23%) and the least was esophageal varices (6%) (table 3). Among the PPIs, pantoprazole (48%) was most commonly prescribed followed

by rabeprazole (34%) and esomeprazole (18%) (Figure 1).

In the treatment of patients with *H. pylori* infection, commonly prescribed kits were Esomperazole kits (54%) followed by pantoprazzole kits (46%). The constituents of the Esomeprazole kit are Esomeprazole 40 mg, Clarithromycin 500 mg, Amoxicillin 750 mg and that of Pantoprazole HP kit are Pantoprazole 40 mg, Clarithromycin 500mg and Amoxicillin 750 mg.

Among the patients with gastrointestinal disorders, the commonly prescribed drug along with PPIs were Domperidone (24%), Drotaverine (21%) and Sucralfate (20%) (Figure 2)

Table 3: Distribution Gastrointestinal disorders

Gastrointestinal disorders	%
Gastritis	23
Gastric & Duodenal ulcers	29
H pyloric infection	19
GERD	14
Esophagitis	9
Esophageal varices	6

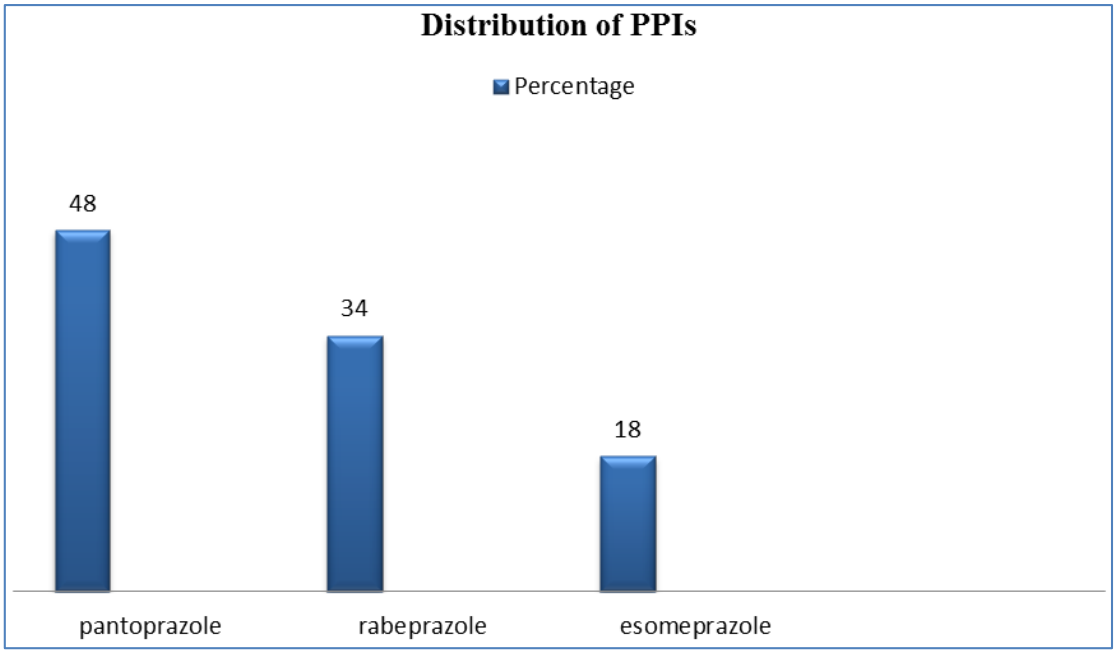

Fig 1: Distribution of PPIs

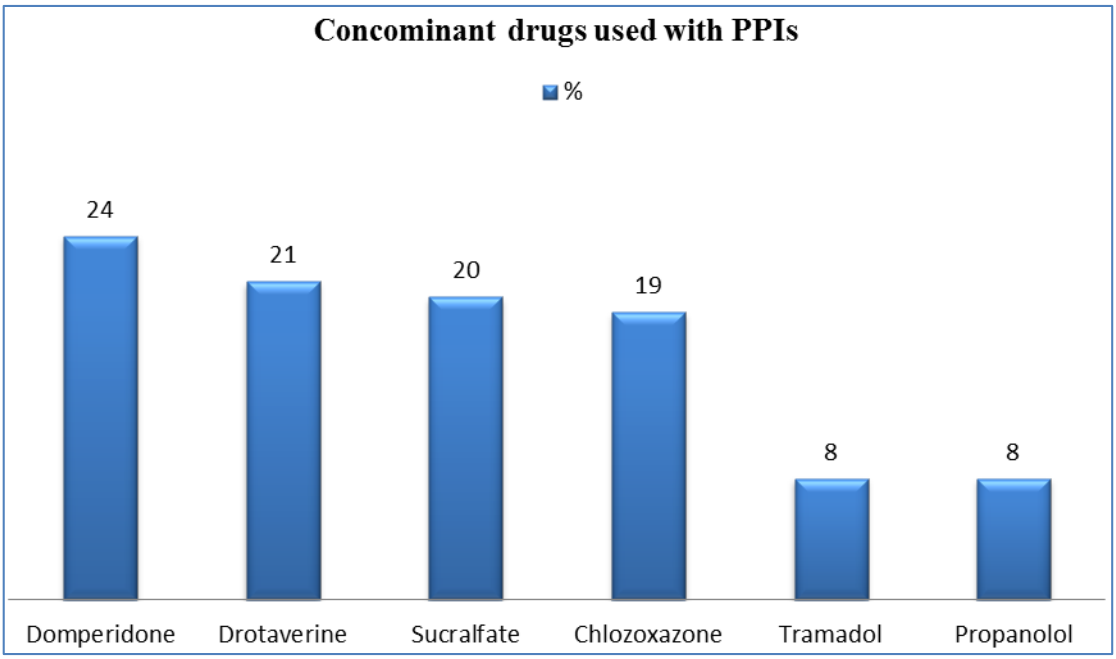

Fig 2: Concomitant drugs used with PPIs

Discussion

Age and gender: In the present study among 190 patients, gastrointestinal disorders were common in male (59%) compared to female (41%). This is identical to the study conducted by *Krishna Kumar Jha et al.* 2016 [3], where male were 55.75% and female patients were 46.25%. The probable reason may be due to social habits, stress and irregular meals eating habits. Peak incidence was observed in 41-50 years of age group (26%) followed by 51-60 years of age group (20%), it is identical to the study conducted by *Jemi Elza*

Varkey et al. 2018 [1] where the 40-60 years age group (34%) was observed followed by 60-80 years (33%).

In this study, PPIs are most commonly prescribed in the gastric and duodenal ulcer (29%) followed by gastritis (23%) which is in contrary to the study conducted by *Vipin kumar singh et al.* 2011 [7] where in PPIs were prescribed in 46% of patients with GERD and 42% patients with dyspepsia.

Pharmacotherapy

Mono therapy of PPIs (84%) were prescribed more than combination therapy of PPIs with prokinetics (16%) which is similar to the *Jemi Elza Varkey et al.* 2018 [1] study where in monotherapy was (55%) and combination therapy was (45%). Combination therapy includes use of prokinetics like domperidone when patients had complaints of nausea, belching and fullness of stomach.

In this study PPIs prescribed the most commonly used PPI was pantoprazole (48%) followed by rabeprazole (34%) and esomeprazole (18%) which is similar to the study conducted by *Shivashankar V et al.* 2016 [8] in which pantoprazole was prescribed in 69% compared to esomeprazole 22%. Our study is in contrary to the study conducted by *Jayaram et al., 2014* [9] where esomeprazole (45%) was most preferred followed by pantoprazole (23%) and rabeprazole (21%). As pantoprazole is listed in National List of Essential Medicines NLEM [10] and due to its efficacy and low cost pantoprazole is the most preferred drug over rabeprzole and esomeprazole.

In our study, among patients with *H.* pyloric infection (19%) the treatment includes the use of *H.* pyloric kits. Among them esomeprazole kit 54% was most commonly prescribed compared to pantoprazole kits (46%). This is similar to the study conducted by *Jayaram et al., 2014* [9] where esomeprazole kits were more commonly used (59.7%) than pantoprazole 39.3%. Esomeprazole kits have good efficacy and is most effective against *H.* pylori infection and controls the infection very rapidly compared to pantoprazole kit and is also the most prefered kits according to FDA prescribing guidelines [5].

In the present study, concomitantly prescribed drugs with PPI are Domperdione (24%) followed by drotaverine (21%) and sucralfate (20%) where as in a study conducted by *Nasrin Shahsavani et al.* 2016 [4] the commonly used medications with PPIs are metformin (31.16%) followed by insulin (29.65%), glipizide (18.18%) as patients had comorbid conditions. The use of Prokinetic agents such as Domperidone or Metoclopramide in short course of 2 to 8 weeks, shows beneficial effect at reducing dyspeptic symptoms [11], whereas drotaverine, chlorzoxazone and tramadol are the centrally acting agents given to control the pain associated with gastrointestinal problems. Sucralfate, a complex of aluminum hydroxide and sulfated sucrose, is a cytoprotective agent that provides a physical barrier over the surface of a gastric ulcer and enhances the gastric mucosal protective system.

Conclusion

We observed that gastrointestinal disorders were most commonly seen in male patients and it was seen more in the age group 41-50 years. The most commonly seen gastric disorders were gastric ulcer and gastritis and the most commonly prescribed PPIs were patoprazole followed by rabeprazole. *H.*pyrolic infections were treated mostly with esomeprazole kits. The usage of pantoprazole was more as it was the most preferred drug in the majority of the gastric disorders observed and also it is one of the recommended drugs by NLEM. The concomitant drugs used along with PPIs were to control the symptoms of dyspepsia and pain associated with gastric disorders. Further studies are needed to analyze the appropriate prescribing pattern of PPIs in gastrointestinal disorders. Clinical pharmacist plays a major role in choosing rationale treatment, monitoring drug therapy and also educating the patients regarding the usage of PPIs in different health conditions.

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