Original Article

Drug Utilization Pattern of Proton Pump Inhibitors at a Tertiary Care Hospital in South India

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Objectives : Evaluate Proton Pump Inhibitors (PPI) utilization in a tertiary care hospital using questionnaire-based patient self-assessment of symptom control, Quality of Life (QoL), and PPI use and safety.

Methods : This cross-sectional study included inpatients with a diagnosis of acid-peptic disease, Gastroesophageal Reflux Disease (GERD), or oesophagitis and those who were on oral or parenteral PPI therapy. Inpatients were categorized as those receiving long-term PPI therapy and those started on PPI therapy after admission. Demographic data from the inpatients,diagnosis, and comorbidities, were recorded. Self-administered questionnaires for symptom control, PPI use, adverse effects and QoL were completed by all patients. Details of prescribed drugs, their brands, dosage, and the route of drug administration were also recorded.

Results : The study included 228 inpatients with ages ranging between 16-88 years. A total of 215 (94.30%) patients were on 40 mg Pantoprazole and received an intravenous administration once a day (132, 57.89%). Among patients who were prescribed PPI upon admission, moderate levels of abdominal and epigastric pain were reported. The mean QoL score among inpatients was 137.54 (34.78%). Most of the patients with heartburn or burning sensation in the chest were prescribed PPI (11, 47.83%).

Conclusion : In the present study, patients were appropriately prescribed PPI for acid reflux or regurgitation and other acid-related symptoms. PPI was not overutilized as most of the patients maintained the prescribed dose of once every day and most of the patients did not report any adverse events. The patients also reported improved QoL with PPI use.

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Key words **: GERD, Peptic Ulcer, Prescription, Proton Pump Inhibitors, Quality of Life.**

Since its introduction 25 years ago, Proton Pump Inhibitors (PPIs) are the mainstay for treating acid-related disorders and further have been the first line of treatment for conditions such as esophagitis, Gastroesophageal Reflux Disease (GERD), peptic ulcer, Non-steroidal Anti-inflammatory (NSAID)-induced ulcer and for part of *Helicobacter pylori* infection treatment[1,2]. PPIs have also been used as an adjunct for patients at risk of gastrointestinal bleeding, functional dyspepsia and eosinophilic esophagitis during antiplatelet therapy[1-3].

PPI reduces the acid secretion from the parietal cells of the stomach, by binding irreversibly to the sulfhydryl groups of cysteines in the H^+/K^+- ATPase enzyme or the proton pump and inactivates this proton pump responsible for acid secretion[2,4]. In general, few adverse events have been reported, therefore making it easily available as an over-the-counter drug in many countries[4].

Editor's Comment :

- Proton Pump Inhibitors (PPIs) are commonly prescribed and safe for acid-related disorders, improving patients' Quality of Life.
- PPIs are mostly used appropriately and prescribed for heartburn and acid reflux, with low adverse events.
- Excessive and inappropriate long-term PPI use can lead to risks like pneumonia, chronic kidney disease, and dementia.

An expert review from India recommends the use of PPI for GERD and acid-related disorders for a minimum of 12 weeks and a total of up to 48 weeks for symptom control[5]. PPIs are among the most prescribed drugs in the world, as it is prescribed for various conditions[6]. Use of PPIs ranged from 46% to a whopping 90% across India, among which 40%-70% of the cases are improperly used or prescribed[7,8]. Literature confirms that PPIs are used excessively and 25%-70% of the times due to inappropriate indications[9].

Excessive and long-term use of PPIs increases the risk of pneumonia, chronic kidney disease, *Clostridium difficiles* infection and even dementia compared to patients with less or no exposure[9].

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Depending on their interactions with other biological mechanisms, PPIs are also known to increase the risk of cardiovascular diseases like endothelial dysfunction[4].

The prevalence of GERD in India ranges between 5%-28.5%[10]. With PPI being the mainstay of treatment for these patients[5], there are very few studies[8] identifying the usage pattern and overutilization in south India. Therefore, we aimed to evaluate the utilization of PPIs among inpatients of a tertiary care hospital in south India,using questionnaire-based patient's self-assessment of symptom control, Quality of Life (QoL), and parameters of prescribed PPI use and safety.

Materials and Methods

This was a cross-sectional study conducted at the Department of General Medicine and Gastroenterology of a tertiary care teaching hospital in south India. The study was approved by Institutional Human Ethics Committee (IHEC) with approval ID PSG/IHEC/2018/Appr/Exp/148 dated June 04, 2018.

The study included adults above 18 years of age, who provided written informed consent to participate. Inpatients with a diagnosis of acid-peptic disease, GERD, or oesophagitis, on oral or parenteral PPI therapy were included in the study. Patients admitted in critical care units, with renal or liver failure, with known Gastrointestinal (GI) tumors or malignancies, diagnosed with *Helicobacter pylori* administered PPI as a combination in a multi-drug regimen and pregnant and lactating women were excluded from the study.

Inpatients were categorized as those receiving long-term PPI therapy and those started on PPI therapy after admission. Demographic data from the inpatients, including age, sex, body weight, Body Mass Index (BMI), socio-economic status, diagnosis and comorbidities, were recorded. Pre-validated questionnaires for symptom control[11], PPI use, adverse effects[12] and QoL[13] were administered to all patients by two trained clinical pharmacists. Details of prescribed drugs, their brands, dosage and route of administration were also recorded.

Based on World Health Organization's (WHO) guidelines for drug utilization study, following relevant WHO prescribing indicators were included[14] :

(1) Average number of drugs per encounter determined by dividing the total number of different drug products prescribed, by the number of encounters surveyed.

(2) Percentage of drugs prescribed by the generic name obtained by dividing the number of drugs prescribed by the generic name by the total number of drugs prescribed and expressed as a percentage.

(3) Percentage of drugs prescribed from essential drugs list was calculated by dividing the number of products prescribed which were on the essential drugs list divided by the total number of products prescribed and multiplied by 100.

Other definitions as per WHO as given below[14]:

The Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD) are defined by WHO for each drug for specific routes of administration and DDD as the average maintenance dose per day which is used as a comparable unit for use in drug utilisation studies. Prescribed Daily Dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions. The PDD measures the average daily amount of a drug that is actually prescribed and PDD is not always equal to DDD. PDD/DDD ratio provides an account of the discrepancies in the prescribed and defined daily doses, thereby reflecting the dosing patterns of prescribed drugs.

The Drug Utilization percentage (DU%) indicator ranks the drugs in a specific pharmacological group and utilization of a specific drug as a total percentage of its therapeutic class can be helpful to represent its clinical use in patient population.

For patients who were started on PPI therapy after admission, the GI symptom questionnaire along with the details of PPI therapy in addition to the demographic and drug-related details was collected. GI symptom questionnaire assessed the symptom severity in the past four weeks and was scored on a scale of 1-7, 1 being no symptom to 7 being unbearable[11]. The symptoms in patients with GERD were assessed using the Frequency Scale for the Symptoms of GERD (FSSG) questionnaire that is used for both diagnosis and assessing treatment effectiveness[15]. Scoring was done on a scale of 0-4, where 0 means no symptoms with4 being always.

The QoL was assessed using the 25-item QoL in Reflux and Dyspepsia (QoLRAD) questionnaire[13] where emotional, sleep disturbances, vitality, difficulties with food/drink and physical or social functioning were assessed using a 7-point Likert scale. A higher total score indicated better functioning, while lower scores meant poor QoL.

Statistical Analysis :

Data were analyzed using Microsoft Excel 2021 (Office 365, Microsoft Corporation). A descriptive analysis of inpatients receiving PPI therapy with definitive indication and empirical therapy was done.

The data were summarized as mean (standard deviation, SD) in the case of continuous variables and as frequency and percentages for categorical data.

Results

The study included 228 inpatients with ages ranging between 16-88 years (mean± SD, 48.55±15.92 years). Most of the patients were women (143, 62.72%). Other demographic characteristics of the inpatients are enlisted in Table 1. A majority of the patients had a history of alcohol intake (173, 75.88%) and missing a meal (198, 86.84%), while few of them had a history of smoking (31, 13.60%), consuming Tea or Coffee (35, 15.35%), Spicy food (34, 14.91%) and delayed or untimely meal (46, 20.18%). A total of 215 (94.30%) patients were prescribed 40 mg Pantoprazole. The remaining patients were prescribed40mg Esomeprazole (5, 2.19%), 20mg Rabeprazole (5, 2.19%) and 20mg Esomeprazole (4, 1.75%). With respect to the route of administration, most of them received an intravenous administration once a day (132, 57.89%), followed by 83 (36.40%) patients who were administered the drug orally, once a day.

Table 1 — *Demographic summary of Inpatients*

Variable	Sub-category	n	%
Sex#	Female	143	62.72
	Male	84	36.84
Occupation#	Professional	55	24.12
	Business	31	13.60
	Homemaker	27	11.84
	Farmer	21	9.21
	Semi-professional	18	7.89
	Others	74	32.46
Residence#	Urban	214	93.86
	Semi-urban	3	1.32
	Rural	9	3.95
History of smoking	Yes	31	13.60
	No	197	86.40
History of alcohol intake	Yes	173	75.88
	No	55	24.12
History of tea or coffee intake	Yes	35	15.35
	No	193	84.65
Spicy food intake	Yes	34	14.91
	No	194	85.09
Missing meal	Yes	198	86.84
	No	30	13.16
Delayed or untimely meal	Yes	46	20.18
	No	182	79.82
Reason for missing or delayed or untimely meal	Nil	183	80.26
	Work-related	34	14.91
	Others	11	4.82
Count of past illnesses (GERD/ acid related / GI disorders only)	Nil	222	97.37
	GERD	2	0.88
	GI disorder	1	0.44
	Acid related	3	1.32
NSAID	Yes (Use of analgesics)	18	7.89
	No	210	92.11
Iron/ vitamin	Yes (Folic acid, vitamin C, and multivitamins)	4	1.75
	No	224	98.25
PPI*	Pantoprazole 40 mg	215	94.30
	Esomeprazole 40mg	5	2.19
	Rabeprazole 20mg	5	2.19
	Esomeprazole 20mg	4	1.75
Route	IV OD	132	57.89
	PO OD	83	36.40
	IV BD	9	3.95
	PO BD	4	1.75

Note : The total may not be 100% due to the presence of missing data (#) or more than one type of medication in certain participants (*). GERD-Gastroesophageal Reflux Disease, PO-Per Orally, IV-Intravenous, OD- Once a Day, BD- two times a day, PPI-Proton-Pump Inhibitors.

It was found that a total number of drug products (n=1247) had been prescribed in the 228 patient encounters and thus, the average number of drugs per prescription was 5.47. Only a minimal proportion of patients (n=7) received a fixed-dose combination of pantoprazole with prokinetic drug domperidone. With respect to generic prescribing, the study recorded a very low percentage of 13.31% indicating that the current prescribing pattern of clinicians favoured prescribing by brand names rather than using generic ones. It was interesting to find that among the 1247 drug products prescribed, an overall 86.26% adherence to the Essential Drugs List (EDL) was evident (Table 2).

The presentation of different symptoms among patients who were prescribed PPI at admission has been listed in Table 3. Moderate levels of abdominal and epigastric pain were reported by all the patients. Stomach rumbling was severe in all of them. Most of the patients did not have any co-morbidities (102, 44.74%), except a small fraction. Few of them had hypertension (29, 13.6%), diabetes mellitus (38, 16.67%), hypothyroidism (11, 4.82%) observed as significant comorbidities.The mean± SD symptom scores of patients with GERD are mentioned in Table 4. High mean scores were reported for heartburn (2.25±0.70), bloating (1.37±0.74), and heartburn after meals (1.25±0.7).

The mean QoL score among inpatients was 137.54 (34.78). A split of scores among different items of the 25-item QoL questionnaire is provided in Table 5. A majority of the patients did not show any impairment when assessed for the ability to bend (101, 44.3%), GI symptoms due to eating or drinking (115, 50.44%),

Table 2 — *Prescribed Daily Dose/Defined Daily Dose ratio for PPI use*

PPI (n)	Anatomical Therapeutic Chemical	PDD (mg/day)	DDD (mg/day)	PDD/ DDD
Pantoprazole (n= 215)	A02BC02	42.23	40	1.055
Rabeprazole (n=4)	A02BC04	20	20	1
Esomeprazole(n=9)	A02BC05	33.33	30	1.11

Table 3 — *Presentation of symptoms among inpatients started on PPI use at admission*

Symptoms	Type of presentation in the IP
Abdominal pain (General)	Moderate
Abdominal pain (postprandial)	Moderate
Abdominal pain (Fasting)	Moderate
Abdominal pain (doesn't decline after defecation)	Moderate
Epigastric pain (general)	Moderate
Epigastric pain (daytime)	Moderate
Epigastric pain (night/asleep)	Moderate
Heart burn	Mild
Regurgitation	Mild
Rumbling	Severe
Bloating	None
Empty feeling	None
Nausea	Mild
Vomiting	None
Loss of appetite	Mild
Postprandial fullness	None
Belching	None
Flatulence	None
Hematemesis	None
Dysphagia (liquid food)	None
Dysphagia (solid food)	None
Symptoms related to stool formation	None
Pain analog scale (0 as no complaints and 10 as unbearable pain)	Score 8

Note : All the patients showed same level of presentation with respect to each symptom

ability to spend time with family or friends (121, 53.07%), eating foods they liked (118, 51.75%), waking up well rested in the morning (120. 52.63%), etc.

Table 4 — *Mean (SD) GERD symptom scores among inpatients*

Symptoms	Mean Score	Standard Deviation
Heartburn	2.25	0.70
Bloating	1.37	0.74
Heavy after meals	1.13	0.64
Rub your chest	0.63	0.74
Sick after meals	0.25	0.46
Heartburn after meals	1.25	0.7
Unusual sensation in throat	0.5	0.53
Full while eating	1	0.92
Stuck while swallowing	0	0
Acid in mouth	0.13	0.35
Burp a lot	0.63	1.06
Heartburn while bending	0.88	0.83
Total score	10	3.29

Among 228 inpatients, 23 of them had a history of long-term PPI therapy. Almost 96% (n=22) of patients in this category were under PPI prescription every day. Most of them took the drug before the manifestation of symptoms (21, 91.30%). Most of the patients with heartburn or burning sensation in the chest were prescribed PPI (11, 47.83%) and seven of them received it as prophylaxis (30.43%).All except one patient did not experience any adverse events after PPI therapy. The history of the use of PPI and its safety among these patients are given in Table 6.

Discussion

PPIs, while considered a safe medication of choice for several acid-related disorders, are overutilized and prescribed without proper indications[3]. The present

Table 5 — *Quality of life scores among inpatients*

Variables	Impaired QoL		Borderline impairment		No impairment	
	n	%	n	%	n	%
Feeling tired or worn out	66	28.95	82	35.96	79	34.65
Felt Generally Unwell	32	14.04	88	38.60	87	38.16
Avoid bending over	41	17.98	85	37.28	101	44.3
GI Symptoms because of eating or drinking	34	14.91	78	34.21	115	50.44
Food seems unappealing	70	30.70	69	30.26	88	38.6
You had to eat less than usual	77	33.77	64	28.07	86	37.72
Avoid doing things with family or friends?	19	8.33	87	38.16	121	53.07
Lack of energy	60	26.32	73	32.02	94	41.23
It was difficult to eat any of the foods or snacks you like?	29	12.72	79	34.65	118	51.75
Lack of sleep / Difficulty in getting a good night's sleep	51	22.37	70	30.70	106	46.49
You have trouble getting to sleep	55	24.12	64	28.07	108	47.37
Wake you up at night and prevent you from falling asleep again?	49	21.49	66	28.95	112	49.12
Fail to wake up in the morning feeling fresh and rested	39	17.11	68	29.82	120	52.63
Discouraged Or distressed	24	10.53	100	43.86	103	45.18
Felt frustrated or impatient or irritable	22	9.65	97	42.54	108	47.37
Felt difficulty in concentrating	24	10.53	101	44.30	102	44.74
Anxious or upset	34	14.91	95	41.67	98	42.98
Had any worries or fears about your health	33	14.47	92	40.35	101	44.3
Avoid certain food,	36	15.79	76	33.33	115	50.44
Avoid certain beverages or drinks	31	13.60	79	34.65	117	51.32
Feel frustrated because the exact cause of your symptoms is not known	26	11.40	79	34.65	122	53.51
Difficulty socializing with family or friends	10	4.39	88	38.60	129	56.58
Avoid eating in restaurant / friend's house	45	19.74	69	30.26	113	49.56
Unable to carry out your daily activities	41	17.98	74	32.46	112	49.12
Unable to carry out your normal physical activities	36	15.79	78	34.21	112	49.12

Table 6 — *History of PPI use and safety among inpatients with long-term PPI therapy*

Variable	Sub-category	n=23	%
How often do you use the prescribed PPI?	Every day	22	95.65
	4 to 6 days per week	1	4.35
On those days, how many times a day do you take?	Once a day	16	69.57
	Twice a day	5	21.74
	Three or more times a day	2	8.70
How often did your doctor tell you to take it?	Once a day	17	73.91
	Twice a day	5	21.74
	Three or more times a day	1	4.35
When you usually use the prescribed PPI?	Only before your symptoms start	21	91.30
	Only after your symptoms start	1	4.35
	Nil	1	4.35
Do you typically take PPI at the same time of day?	Morning	23	100.00
Are there any breakthrough symptoms?	Yes	9	39.13
	No	14	60.87
What are the breakthrough symptoms do you get? #	Nil	17	73.91
	Regurgitation	2	8.70
	Heartburn	4	17.39
	Pain abdomen	1	4.35
At which time do you get breakthrough symptoms?#	Nil	16	69.57
	Afternoon	3	13.04
	Noon	1	4.35
	Morning	1	4.35
	Daytime	3	13.04
What condition or conditions did the doctor prescribe PPI?#	Heartburn/burning feeling in chest	11	47.83
	Reflux/acid reflux	8	34.78
	Acid indigestion/acid in stomach	4	17.39
	Upset stomach	2	8.70
	Stomach or intestinal cramps or pain	3	13.04
	Hiatal hernia	0	0.00
	Ulcer	4	17.39
	GERD/Gastroesophageal Reflux Disease	4	17.39
	Acid feeling in throat	3	13.04
	Prophylaxis	7	30.43
	Jaundice	1	4.35
	HCV-related liver cirrhosis	1	4.35
	Prophylaxis - pancreatitis	1	4.35
How satisfied are you with PPI? ("10" means feeling extremely safe and "0" means feeling not safe at all)	0-4	0	0.00
	5	1	4.35
	6	1	4.35
	7	2	8.70
	8	7	30.43
	9	9	39.13
	10	3	13.04
Have you ever taken any non-prescription remedies such as antacids?	Yes	0	0.00
	No	23	100.0
Have you taken a non-prescription remedy and PPI during the same day?	Yes	0	0.00
	No	23	100.00
Have you experienced any of these adverse effects after being started on PPI therapy?	Yes	1	4.35
	No	22	95.65

Note : # more than one presentation in certain patients. The adverse effect reported was pain abdomen about 2 to 6 times per week

study evaluates the utilization pattern of PPIs among inpatients of a tertiary care hospital in south India.

All the patients in the present study were undergoing PPI therapy for various acid-related disorders and almost 95% of them were on 40 mg of Pantoprazole. On assessing the pattern of utilization of PPIs in these patients, we observed that the majority of them used a PPI once daily, as prescribed by the physician.Most of the patients in the present cohort took the medication before the onset of symptoms. Overall, the majority of the patients were satisfied with the PPI therapy prescribed.The pattern of utilization of PPI was previously studied by Tadvi N, *et al* 2014, in Andhra Pradesh, India[7]. Drawing similarities to the current study, Tadvi N, *et al* 2014, reported Pantoprazole as a commonly prescribed PPI and a once-daily frequency of PPI use by a majority of the patients[7]. While in the present study, there was no inappropriate indication of PPI as it was predominantly prescribed for heartburn and acid reflux conditions, a study conducted on hospitalized patients reported an inappropriate indication in about 61.5% of the patients[16]. However, inappropriate prescription volume varies across geographies, as observed by different studies conducted in Saudi Arabia, Shanghai, Canada,etc., where PPI was inappropriately prescribed in 6.5%, 50% and 20.3%, respectively[17-19]. We also observed that the PDD/DDD ratio was close to 1 indicating an adequate prescription as there was no difference in the actual dosage and recommended dosage. However, different studies, including global trends and practices report a higher prescribed dose, ie, a dose higher than DDD[18,20].

Generic medicines play a key role in providing cost-effective health care. Generic medicines account for over 80 per cent of medicines prescribed in countries like USA, UK, China and Australia. In India, however,

generic prescribing is often lesser than 50 per cent. The primary advantage of unbranded generics is their lower cost. But the major concern is the lack of confidence of physician and patients in their quality[21]. Enforcement of strict generic prescribing without a parallel stringent system to ensure quality of generic medicines can impact patient safety and care and hence this has been voiced by the doctor fraternity through the Indian Medical Association (IMA)[22]. In the current study, prescription adherence to National List of Essential Medicines (NLEM) was 86.26% which was relatively higher in comparison to a recent study evaluating the extent and pattern of prescribing drugs not included in NLEM at 13 tertiary care hospitals across India in which about a third 31.12% of the total drugs prescribed were not included in the NLEM[23].

In the present study, a group of patients who were not under long-term use of PPI and were prescribed the same at the time of admission, presented with severe rumbling, moderate abdominal and epigastric pain, mild heartburn, regurgitation, nausea, appetite loss, which are typical symptoms of peptic ulcer disease[24]. Among the eight inpatients who were already under PPI therapy and diagnosed with GERD, heartburn, bloating, the feeling of heaviness after meals, and heartburn after meals were commonly reported symptoms. A mean FSSG score of 10(SD=3.29) was observed in the present cohort. This was similar to a study conducted in Japan which reported a mean (SD) FSSG score of 9(7.3) among PPI users[15].

Regarding adverse effects of PPI, almost 74% of the patients did not report any breakthrough symptoms and 95.65% of the patients did not experience any adverse events. This re-emphasizes the excellent tolerability of PPIs with fewer side effects and this trend of very few to no adverse symptoms could also be attributed to the rational prescription of PPI among the patients in the present study. There is evidence to support the occurrence of adverse events like hypomagnesemia, pneumonia, or even fractures among patients inappropriately prescribed PPI therapy[19].

In the present study, a mean QoL score of 137.54±34.78 indicated better QoL among the PPI users.Patients reported mild to no impairment emotionally, in daily routine activities, physical distress, sleep disturbances, etc. A study conducted in the Turkish population reported a mean QoLRAD score of 96.08±34.76 in patients who had stopped PPI use for 10 days. They confirm that the use of PPI considerably improved the symptoms and hence the QoL[25].

Strengths and Limitations :

The present study is the only study in South India that describes various factors among PPI users including QoL, symptom control and adverse events. However, as it was a single-centre drug-utilization study, this could have induced bias. A cost analysis was not captured in the present study and the study design was cross-sectional rather than a prospective one to compare the effects on outcomes pre- and post PPI therapy. Further studies warrant a comparison of PPI and non-PPI users and symptomatic and non-symptomatic patients with respect to the QoL and other factors.

Conclusion

In the present descriptive study, patients were appropriately prescribed PPI for heartburn or regurgitation and other acid-related symptoms. PPI was not overutilized as most of the patients maintained the prescribed dose once every day.In consensus with the safety of PPI, most of the patients did not report any adverse events. The patients in fact had improved QoL with PPI use.

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