

Drug Utilization and Evaluation of Proton Pump Inhibitors in General Medicine Ward of a Tertiary Care Hospital

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Abstract

Introduction: Proton pump inhibitors (PPIs) are one of the most frequently prescribed classes of drugs. The prescriptions for the PPIs have increased consistently over the past years.

Aim: The objective of this research is to study and evaluate the utilization pattern of PPIs in the inpatient department of general medicine in a south Indian hospital.

Method: A prospective-observational study was conducted out for eight months. The case sheets of the patients were reviewed for PPIs prescription, and relevant data was taken.

Result: A total number of 160 patients, 65.3% of males and 34.7% of females, were included in the study. Most of the patients were in the age group of 50-59 years (25.3%). About 42.4% of the patients were prescribed PPIs for other reasons than those indicated in the National Institute of Clinical Excellence (NICE) guidelines. The majority (78.7%) of the patients were prescribed with pantoprazole. By NICE guidelines, appropriate use of PPIs was found in 64% where as it was inappropriate to use in 36% of cases. Most of the potential drug-drug interactions were moderate. Defined daily dose (DDD)/100 bed day of PPIs was found to be 0.929. The highest average cost per prescription was found for pantoprazole injection (INR 169.81), and the lowest average cost per prescription was found for esomeprazole (INR 14.92). Rabeprazole (20 mg, tablet) showed maximum percentage price variation of 672.32% while pantoprazole (40mg, injection) showed a minimum percentage price variation of 18.72%.

Conclusion: PPIs should be used only when there is documented evidence and when their use is clinically justified so that the appropriate prescription of PPIs will reduce the healthcare burden of the patient. The study is expected to act as an audit and provide evidence to promote the essential and rational use of PPIs.

Keywords: Drug utilization, Proton Pump Inhibitors, DDD/100 bed days, Price variation, NICE guidelines

INTRODUCTION

The World Health Organization (WHO) defines drug utilization research (DUR) as “the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” [1]. The ultimate goal of DUR is to evaluate whether the drug treatment is rational or not which may provide insights into the various aspects of prescribing patterns such as frequency, dosage, duration of therapy, indication quality, determinants and outcome of drug use. DUR is used as a potential tool in the evaluation in the healthcare systems as well as a powerful exploratory tool to explain the role of drugs in the society. PPIs are one among the most commonly prescribed class of medications in both outpatient and inpatient treatments. These medications are used for long-lasting suppression of gastric acid by inhibiting the hydrogen-potassium adenosine triphosphatase enzyme system, which makes the stomach acidic, and it is found in the cells that line the stomach.

Over the past few years, the prescriptions for the Proton Pump Inhibitors (PPIs) have consistently increased in the hospital and ambulatory care settings. Studies have shown that the incidence of irrational use of PPIs ranges for 40-

70% [2]. Such research help in achieving optimal benefits of drug therapy in patient care, which may not be achieved because of underuse, overuse, or misuse of drugs. The National Institute of Clinical Excellence (NICE) guidance recommends indication for prescribing PPIs on: management of Gastro oesophageal Reflux Disease (GERD) and upper gastrointestinal bleeding (including varices), in the management of Barrett's oesophagus, Zollinger-Ellison Syndrome, ulcer healing, Helicobacter pylori eradication, prophylaxis of peptic ulcer disease for patients taking Non-steroidal Anti-inflammatory Disease (NSAIDs)/aspirin/steroid, prophylaxis for patients taking anticoagulants, Second-line for non-ulcer dyspepsia (i.e., dyspeptic symptoms with normal endoscopic findings) and prophylaxis of stress ulcers. The guidelines suggest that PPIs should be started or continued only at intermittent courses, and they should be used to control symptoms or promote healing, typically up to 4-8 weeks [3].

The recent literature review has shown inappropriate use of PPIs has increased the risk for adverse drug reactions (ADRs) and drug interactions [4], PPIs are being over utilised because of the easy availability, high efficacy, competitive marketing and expanded indications [5]. The various side effects of PPIs are constipation, headache,

abdominal pain, flatulence, and diarrhoea, which are mild and self-limiting. Long-term effects include *Clostridium difficile* infection, gastric carcinoids, hypomagnesaemia, and increased risks of hip fractures [4]. PPIs get metabolized through cytochrome P450 and lead to drug interactions by increasing their half-life and thus causing harmful systemic effects [6]. In the current setting, the consumption of PPIs is overwhelming; studies have to be carried out to examine the prescribing pattern of the PPIs in hospitalized patients. Hence, the present study aimed to assess and evaluate the utilization patterns of PPIs in the inpatient department of general medicine of a tertiary care hospital.

MATERIALS AND METHODS

Study design, site, and ethical approval

A prospective observational study was carried out for a period of 8 months from August 2016 to March 2017 in inpatient department of general medicine of Justice K.S. Hegde Charitable Hospital, a 1200-bedded private tertiary hospital centrally located in Dakshina Kannada district, Mangaluru. The research was approved by the institutional ethical committee of Nitte (Deemed to be University), Mangalore (REF: INST.EC/EC/68/2016-17) before the study.

Sample size

A total number of 170 sample population were selected for the study.

$$N = \frac{Z^2_{1-\alpha/2} P (1-P)}{D^2_{\alpha}}$$

Where,

Z- 1.96

α - Level of significance (5%)

D- Precision (10%)

P- Population proportion (53%)

N- Number of patients

Hence, the minimum sample size required for the study was approximately 100.

Study criteria

Inpatients of both gender and age group for more than 18 years, prescribed with PPIs were included for the study. Outpatients prescribed with PPIs and patients with psychiatric conditions, lactating and pregnant women were excluded from the study.

Data collection

The patient data collection form was designed as per the need of the study. The patients were reviewed as per inclusion criteria, voluntarily informed consent was taken, and necessary data were collected. Which includes the age, gender, social history, past medical history, family history, history of PPIs, laboratory data and medication charts (name of drug, dosage form, frequency, route of administration and duration of treatment), cost per dose, cost/day and cost during the length of hospital stay.

Data analysis

Prescribing Pattern, Drug interaction, and Cost.

Prescribing patterns of the PPIs were analysed by

collecting the details of drug usage, including frequency, route of administration, dosage form, duration of treatment, indications, and continuation after discharge. The appropriateness of PPIs was evaluated using NICE guidelines. The potential drug-drug interactions were identified by using the software's, namely Micromedex and Medscape drug interaction checker and were categorized based on their severity. The cost was analysed by considering parameters like brands of PPIs used, frequency, dosage and length of hospital stay which were collected from the patient records, medical bills, hospital accounts section and interviewing the patients or patient parties. The PPIs were classified according to the ATC system, and the consumption was measured by using DDD/100 bed days and compared with WHO standards Shelat P.R et al., (2015) [14, 17].

Price variation Analysis of different brands of PPIs:

The hospital pharmacy department and the Current Index of Medical Specialities (October 2016-January 2017) were used for the price variation analysis of the different brands of PPIs. Cost/tablet of a particular drug of various dosage forms and strengths, manufactured by different companies were compared. Drugs with only one brand available were excluded. Cost differences between the minimum and maximum costs of the similar drugs were calculated. Percentage price variation for all brands of PPIs was calculated by using the same method of Patel D. et al., (2009) [16].

Statistical analysis

Data were analysed using descriptive statistics. Continuous data were expressed as mean \pm S.D., and the nominal data were expressed as percentages. Analysis of the data was carried out by using Statistical Package for Social Science (SPSS) 16.0 for windows.

RESULTS

Demographic details of the patients

Out of 170, most of the patients were in the age group of 50-59 years 43 (25.3%), followed by 60-69 years 40(23.5%) and other age groups. The mean age of the study population was 52.3 \pm 15.3 years. The age wise distributions of patients treated with PPIs are summarized in the Table1. In the study population, 111 were male patients who constituted 65.3%, and 59 were female patients who represented 34.7%. The details are illustrated in table 1.

Table 1: Age wise distribution of patients

Age group (years)	Number of patients (N=170)	Percentage (%)
18-29	15	8.8
30-39	20	11.8
40-49	28	16.5
50-59	43	25.3
60-69	40	23.5
≥ 70	24	14.1

Duration of hospital stay

In this study, the percentage of the length of hospital stay for 1-10 days was found in 147 patients (86.5%), for 11-20 days in 20 patients (11.8%) and 21-30 days in 3 patients (1.8%). The median length of hospital stay of the study population was 6.00± 4.03.

Indications and utilization for PPIs

During the study period, most of the patients were prescribed PPIs for other reasons than those indicated in NICE guidelines (42.4%), followed by 27.6% of PPIs were prescribed along with NSAIDs. The indications for prescribing PPIs are summarized in Table 2.

Table 2: Indications for prescribing PPIs

Indications	Number of Patients (N=170)	Percentage (%)
Peptic ulcer disease	8	4.7
GERD	6	3.5
Dyspepsia	1	6
Gastritis	4	2.4
NSAIDS	47	27.6
Concomitant use of steroid	20	11.8
Concomitant use of warfarin	1	.6
Concomitant use of the antiplatelet drug	11	6.5
Others*	72	42.4

*Others- Diabetes, gastroenteritis, viral fever, pancreatitis, hypertension, anaemia, bronchial asthma, COPD, hyperthyroidism, cirrhosis of liver, malaria, pulmonary tuberculosis.

Continuation of PPIs after discharge

In this study, the percentage of continuation of PPIs for <1 week was found to be 35 (20.6%), 1-2 week 69 (40.6%), 3-4 week 27 (15.9%) and discontinued the PPI therapy after discharge 39 (22.9%).

Appropriateness of PPIs

According to the NICE guidelines, the appropriate use of PPIs was found in 109 patients (64%), whereas inappropriate use of PPIs was found in 61 patients (36%).

Concurrent drugs prescribed

In the study population, anti-infectives were the most commonly prescribed drugs (22.5%), followed by cardiovascular drugs (17.2%) and multivitamin/mineral/supplements (11.2%). The detailed description of concurrent medicines prescribed is summarized in Table 3.

Drug interactions of PPIs with other drugs**Frequency and outcomes of potential drug-drug interactions**

Majority of drug-drug interactions was caused by atorvastatin + pantoprazole 25 (16.8%), followed by propranolol + pantoprazole 19 (10.7%). The frequency and

outcomes of the potential drug-drug interactions involving PPIs are summarized in Table 4.

Table 3: Distribution pattern of concurrent drugs

Concurrent Drugs	Number (N= 1684)	Percentage (%)
Antidiabetics	96	5.7
Cardiovascular	289	17.2
Antiasthmatics	134	8
Cold/Cough/ Antiallergics	80	4.8
Anti-infectives	378	22.5
GIT drugs	78	4.6
Antiemetics	65	3.9
Steroids	70	4.2
Anticoagulant/ Antiplatelet	47	2.8
Antiulcerants/ Antacids	20	1.2
CNS drugs	62	3.7
NSAID/ Analgesics	161	9.6
Multivitamins/ mineral / supplements	204	11.8

prescribed with PPIs**Table 4: Frequency and outcomes of potential drug-drug interactions**

PDDIs involving PPIs	Outcomes of interaction	Number (N =149)	Percent age (%)
Atorvastatin+ Pantoprazole	Increased blood levels of atorvastatin	25	16.8
Propranolol + Pantoprazole	Increased propranolol exposure	19	10.7
Torsemide + Pantoprazole	Hypomagnese mia	16	8.7
Torsemide + Rabeprazole	Hypomagnese mia	3	2.0
Furosemide + Pantoprazole	Hypomagnese mia	14	8.1
Glimepiride + Esomeprazole	-	1	0.7
Fluconazole + Pantoprazole	Increased plasma concentration of cyp2c19	2	1.3
Clopidogrel + pantoprazole	Increased effectiveness of clopidogrel	9	6.0
Clopidogrel + Rabeprazole	Increased risk of thrombosis	2	1.3
Fluconazole + Rabeprazole	Increased plasma concentration of cyp2c19	1	0.7
Cefpodoxime + Pantoprazole	Increased blood levels of cefpodoxime	3	2.0
Rifampin + Pantoprazole	Increased blood levels of rifampin	7	4.7
Cyanocobalamin + Pantoprazole	-	4	2.7
Amikacin +	Hypomagnese	1	0.7

PDDIs involving PPIs	Outcomes of interaction	Number (N =149)	Percent age (%)
Pantoprazole	mia		
Ferrous fumarate + Pantoprazole	Increased absorption of iron	9	6.0
Metolazone + Pantoprazole	Hypomagnese mia	1	0.7
Metalazone + Rabeprazole	Hypomagnese mia	2	1.3
Digoxin + Pantoprazole	Increased effects of digoxin	2	1.3
Aspirin + Pantoprazole	-	10	13.4
Atorvastatin + Rabeprazole	Increased blood levels of atorvastatin	2	1.3
Cilostazol + Pantoprazole	Increased cilastazole exposure	2	1.3
Budesonide + Pantoprazole	Decreased effects of budesonide	4	1.3
Theophylline + Pantoprazole	Increased effect of theophylline	9	6.0
Theophylline + Rabeprazole	Increased effect of theophylline	1	0.7

The severity of potential drug-drug interactions

According to severity classification, the majority of the interactions were moderate 130 (87.2%), 15 (10.1%) were minor interactions, and 4 (2.7%) were major interactions.

ATC code and DDD/100 bed days of PPIs prescribed

The usage of PPI was calculated in terms of DDD/100 bed days. The DDD/100 bed day for PPIs was 0.929. Pantoprazole was the most frequently prescribed (0.794 DDD/100 bed days), followed by rabeprazole (0.122 DDD/100 bed days). The ATC code and the DDD/100 bed days of the prescribed PPIs are summarized in Table 5.

Table 5: ATC code and DDD/100 bed days of PPIs prescribed

Drug name	ATC Code	WHO DDD value (mg)	DDD/100 bed days
Pantoprazole	A02BC02	40	0.794
Rabeprazole	A02BC04	20	0.122
Esomeprazole	A02BC05	30	0.013

* The WHO DDD value for ilaprazole, pantoprazole combinations and rabeprazole combinations were not mentioned in ATC/DDD index 2016.

Utilization of PPIs in the general medicine ward

The utilization of PPIs in the general medicine ward during the study period are summarized in Table 6.

Average PPIs cost per prescription

The highest average cost per prescription was found for pantoprazole injection (INR 169.81) followed by

ilaprazole (INR 126.00). The lowest average cost per prescription was found for esomeprazole (INR 14.92). The overall total cost of PPIs was INR 14,020.085. The average PPIs costs per prescription are represented in Table 7.

Table 6: Utilization of PPIs in the general medicine ward

Drugs	Total cost (INR)	% of the total drug cost	No. of prescriptions encountered (N=174)	% of prescriptions	The average cost per prescription (INR)
Pantoprazole tablet	5743.98	40.9	105	60.3	54.70
Pantoprazole injection	5434.20	38.8	32	18.4	169.81
Rabeprazole	1,353.91	9.7	14	8.1	96.70
Ilaprazole	252.00	1.8	2	1.1	126.00
Esomeprazole	89.54	0.6	6	3.4	14.92
Fixed dose combinations	1,146.455	8.2	15	8.7	76.43

Table 7: Average PPIs cost per prescription

Drugs	Formulation	Quantity Used (mg)	Percentage (%)
Pantoprazole	Tablet	32480	71.9
	Injection	6280	13.9
Rabeprazole	Tablet	2920	6.5
Esomeprazole	Tablet	480	1.1
Ilaprazole	Tablet	230	0.5
Pantoprazole + Domperidone	Tablet	2080	4.6
Rabeprazole + Domperidone	Tablet	680	1.5

Mean cost per day between PPIs

The highest mean cost per day was spent by patients who had been prescribed with pantoprazole injection (43.38 ± 20.45) and the lowest mean cost per day was spent by the patients who had been prescribed with esomeprazole (7.5 ± 0.33). The mean costs per day between different PPIs prescribed are summarized in Table 8.

Table 8: Mean cost per day between different PPIs prescribed

Drugs	Cost /day
Pantoprazole tablet	7.35 ± 4.51
Pantoprazole injection	43.38 ± 20.45
Rabeprazole	11.62 ± 6.54
Esomeprazole	7.5 ± 0.33
Ilaprazole	10.5 ± 0.00
Pantoprazole + Domperidone	12.36 ± 5.17
Rabeprazole + Domperidone	11.07 ± 2.09

Table 9: Price variation of different brands of PPIs

Drug	Dosage form	Dose (mg)	Number of brands	Minimum cost (INR)	Maximum cost (INR)	Percentage price variation
Pantoprazole	Tablet	20	4	3.50	6.10	74.28
		40	8	5.292	10.30	94.63
	Injection	40	3	43.38	51.50	18.72
Rabeprazole	Tablet	20	7	1.12	8.65	672.32
Esomeprazole	Tablet	20	2	3.30	3.63	33.00
		40	3	5.50	6.393	16.23
Omeprazole	Tablet	10	2	2.00	2.825	82.5
		20	5	2.425	5.876	142.30
Pantoprazole + Domperidone	Tablet	40/30	9	7.630	15.325	100.85
Rabeprazole + Domperidone	Tablet	20/30	6	6.90	13.7	110.7

Price Variation of different brands of PPIs

The price variations of different brands of PPIs are summarized in Table 9.

DISCUSSION

In this study, most of the patients admitted to the inpatient department of general medicine were in the age group of 50-59 years (25.3%), while in the study conducted by Mathew et al., (2015) most of the patients were in the age group of 60-80 years (42.16%) which showed that elderly patients were more [7]. The percentage of male patients (65.3%) in the study was more when compared to female patients (34.7%). These findings were similar in the studies conducted by Mathew et al., (2015); Echevarria et al., (2008) where it was reported that males were more than the females [7, 8]. About 47% of the patients were prescribed PPIs along with NSAIDs. Similar results were reported by Nousheen et al., (2014); Patil et al., (2015) [2, 9]. However, these results were in contrary to the study conducted by Kunwar et al., (2015) where PPIs were most commonly prescribed along with NSAIDs (73.85%) [5]. On categorizing the PPI prescriptions, it was observed that pantoprazole (78.7%) was most commonly prescribed in the inpatient department of general medicine. These results were following the study carried out by Kunwar et al., (2015); Rad et al., (2016) (98.70%) [5, 10]. However, contrary results were shown in the study conducted by Ntaios et al., (2009) where they found out that omeprazole was the most commonly prescribed PPI (39.7%). The observed difference was because in the current year's pantoprazole showed better efficacy and lesser side effects [11].

In the present study, majority of the patients were prescribed with oral therapy of PPIs (81.2%), and intravenous PPIs were prescribed to 5.9%, whereas both IV and PO were prescribed to 12.9% of the patients. Similar results were reported in the study conducted by Airee et al., (2016) [4]. The results were in contrast to the survey conducted by Mathew et al., (2015); Neupane et al., (2016) in which the majority of the patients were prescribed with intravenous PPIs. The main reason behind this was the patient's physical condition, not able to

swallow the drug, use of corticosteroids and NSAIDs [7, 12]. The frequency of PPIs on once daily basis was reported in 88.2% patients, twice daily basis in 10% patients and both OD and BD in only 1.8% patients. The findings were similar to Nousheen et al., (2014); Mathew et al., (2015) studies. Most of the PPIs were prescribed on a once daily basis as this was enough to produce the therapeutic effect in the patients [2, 7]. Majority of the patients (40.6%) were prescribed with PPIs for 1-2 weeks even after discharge. This was in contrast with the studies conducted by and Kunwar et al., (2015); Mathew et al., (2015) where the maximum number of PPIs was prescribed for one week after the discharge. The reason behind this was most of the PPIs were prescribed with NSAIDs for one week [5, 7].

In comparison with the NICE guidelines, the appropriate use of PPIs was found in 64% of the patients, whereas inappropriate use was found in 36%. The study conducted by Mathew et al., (2015) showed comparable results whereas in the study conducted by Ramirez et al., (2010) the results were contradictory which reported that the inappropriate use of PPIs was more than the appropriate use. The reason behind this was the majority of the PPIs were prescribed without any valid indications [7, 13]. In our study, PPIs were prescribed in patients with viral fever, COPD, bronchial asthma, hyperparathyroidism during the first day of hospitalization for which there was no valid documented evidence, and this accounted for the inappropriate use. This suggests that although PPIs are the safe and effective class of pharmaceutical agents, they should be used only when there is standard evidence of a gastrointestinal disorder that cannot be treated with an H2-receptor blocker and wherever the use of PPIs is clinically justified. In the future, more of drug utilization studies should be carried out to compare the rationality of use of PPIs and other antisecretory drugs like H2-blockers to know the exact consequence and plan for necessary measures.

In this study, anti-infectives were mostly commonly prescribed concurrent medications (22.5%) which showed similar results to the studies conducted by Nousheen et al., (2014); Airee et al., (2016) [2,4]. According to the severity

classification of drug-drug interactions, the study showed 87% moderate, 10% minor, and 3% major interactions. The results were comparable with those observed in the Airee et al., (2016) study. Major interactions were caused by rabeprazole + clopidogrel, which increased the risk of thrombosis and pantoprazole + cilastazol, which increased the cilastazol exposure [4]. Our study results showed that DDD/100 bed day for PPIs was 0.929. The DDD/100 bed days of pantoprazole was found to be 0.794. A similar study was conducted by Shelat et al., (2015) which showed that the overall consumption of PPIs was 120 DDD/100 bed days because greater utilization rates were observed in the internal medicine and general surgery departments compared to our study which was carried out only in inpatient department of general medicine [14].

This study showed that mean cost per day was high in patients prescribed with pantoprazole injection (43.38 ± 20.45) and the low in the patients prescribed with esomeprazole (7.5 ± 0.33). Similar findings were reported in the study conducted by Nousheen et al., (2014) (2). The findings in our study showed that among the various brands of PPIs available in our hospital pharmacy department, rabeprazole (20 mg, tablet) showed maximum percentage price variation of 672.32% while pantoprazole (40mg, injection) showed minimum percentage price variation of 18.72%. These results were contrary to the study conducted by Kolasani and Divyashanthi et al., (2016) and Patel, D et al., (2009) where pantoprazole (40 mg; EC tablet) showed the highest price variation (500.75%) while omeprazole (40 mg; Injection) showed the least price variation (2.15%) because in this study price variation was done for different brands of PPIs available in the Indian market [15, 16]. Wide variation in the prices of the different brands of PPIs was seen, which will increase the economic burden of the patients [17]. Hence, importance should be given for the prescription of the generic drugs.

CONCLUSION

The present study showed the usage pattern of PPIs in a wide range of indications. During the study period most commonly prescribed, PPI was pantoprazole. Out of 170 patients, appropriate use was found in 64%, and inappropriate use of PPIs was found in 36% of cases. PPIs should be used only when there is valid documented evidence and when their use is clinically justified. The total consumption of PPIs was found to be 0.929 DDD/100 bed day. Various efforts should be made to reduce the unnecessary use of PPIs to minimize drug interactions, related risks, and health care costs. This study showed a wide price variation of PPI brands. Hence there is a need to decrease the variation in the prices, thereby reducing the economic burden on the patients. Finally, this study concludes that the pharmacists and the other medical professionals should work together for the rational use of PPIs by making interventions like the educational programs and institutional specific guidelines should be

developed and implemented to reduce the usage of PPIs in the inpatients.

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