Journal of Pharmaceutical Care
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Pharmacoeconomics and Utilization of Intravenous Proton Pump Inhibitors in a Tertiary Care Hospital

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Received: 2022-07-17, Revised: 2022-08-25, Accepted: 2022-08-27, Published: 2022-09-30

ARTICLE INFO

Article type:
Original article

Keywords:
Pharmacoeconomics;
Stress Ulcer Prophylaxis;
Intravenous Pantoprazole

ABSTRACT

Background: Proton pump inhibitors (PPIs) are one of the most frequently prescribed class of drugs worldwide contributing to the increase in economic burden on the healthcare system. To study the utilization of intravenous proton-pump-inhibitors (PPIs) according to its indications, comorbidities and related pharmacoeconomics in a tertiary care teaching hospital

Methods: A prospective-observational study was conducted over 3 months. Case-records of 300 indoor patients were reviewed for IV (intravenous) pantoprazole prescription, as it was the only PPI available at the hospital in IV as well as oral formulations and relevant data was procured.

Results: Amongst 300 patient records, 72% were males whereas 28% were females and mean age was 41.18 years (S.D. ± 15.91). 37.33% of the patients were prescribed PPIs for Stress ulcer prophylaxis and 62.66% for non-stress ulcer prophylaxis. 62.66% patients were prescribed IV PPIs inappropriately and 74% were found to be potential candidates for oral pantoprazole therapy without affecting patient outcomes. Utilisation of PPIs was found to be 0.87 defined daily dose (DDD)/100 bed days. The cost of administration for intravenous pantoprazole therapy per patient per day accounted to INR 64.34 and that for oral formulation of the same summed up to INR 1.36. The percentage reduction in the cost of administration of PPI therapy per patient in potential candidates for oral PPI therapy was found to be 97.8%. Antimicrobials (36%) were the most common drugs prescribed concomitantly followed by antiemetics (25%).

Conclusion: Subtle changes like shifting the patient to oral formulations when clinically permissible can make a significant positive contribution in resource limited settings without negatively impacting patient outcomes. This will effectively reduce the economic burden on the patients and the healthcare system which is of utmost importance in a resource limited setting like tertiary care hospitals.

J Pharm Care 2022; 10(3): 115-121.

► **Please cite this paper as:**
Kadam P, Tiwari S, Daswani B, Taware A, Hiray R. Pharmacoeconomics and Utilization of Intravenous Proton Pump Inhibitors in a Tertiary Care Hospital. J Pharm Care 2022; 10(3): 115-121.

Introduction

The World Health Organization (WHO) describes drug utilization research (DUR) as "the marketing, distribution, prescription and use of drugs in a society, with special importance on the resulting medical, social and economic consequences" (1). DUR is a simple but convenient tool used to assess healthcare systems and to elucidate the role of drugs in the society.

Proton pump inhibitors (PPIs) remain to be one of the most commonly prescribed class of drugs in both outdoor and indoor patients as they are most potent gastric acid suppressing drugs currently in clinical use. They cause irreversible inhibition of the gastric H^+/K^+ ATPase pump also known as proton pump and reduce both basal and stimulated gastric output (2).

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Indications of intravenous (IV) PPIs are several, including different forms of peptic ulcer disease (Helicobacter pylori associated or not), functional dyspepsia, gastroesophageal reflux, gastrointestinal bleeding prevention in conditions of severe stress and stress ulcer prophylaxis for peptic ulcer disease induced by non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Despite of specific and clear clinical indications, intravenous preparations of PPIs are being used extensively, whether justifiable or not (2).

Literature survey shows that chances of adverse effects like hypomanganesemia and clostridium difficile-associated diarrhoea increase exponentially when PPIs are prescribed on a large scale. Some studies show the association of chronic use of proton pump inhibitors with gastric carcinoids and also an increase in the risk of pelvic fractures. Chronic use of PPIs shows increasing evidence of gastritis and ulcer symptoms, thrombocytopenia, osteoporosis and endocrine disorders such as gynecomastia and impotence (3,4). Another study explains local effects of such therapy which include atrophic gastritis due to prolonged acid suppression or hypergastrinemia, chronic H. pylori infection, and/or development of gastric polyps are also associated with use of PPIs, although these drugs are used for their treatment (5). PPIs are metabolised by cytochrome P450 (CYP3A4, CYP2C19) that also metabolize other drugs, leading to a subtle concern for drug interactions with PPIs especially in patients with chronic diseases.

Parenteral preparations by convention are costlier than their oral counterparts; they thereby increase the economic burden on government and healthcare system. This study was therefore designed to create awareness as regards to the utilization and economic burden in the form of defined daily dose (DDD) per 100 bed days for intravenous PPIs and judicious use of PPIs in clinical practice by determining the percentage of patients who are potential candidates for oral PPI therapy. Appropriate utilization of resources needs to be emphasised on in a resource limited setting such as a busy tertiary care government hospital. Furthermore, determination of appropriateness of IV PPI therapy and thus, finding patients who can be potential candidates for oral PPI therapy will aid in cost cutting. Information thereby obtained from Pharmacoeconomic studies will hence prove beneficial by ensuring apt treatment for the patients and for stakeholders to successfully utilize available resources. Therefore, aim of this study is to deduce the utilization of intravenous proton-pump-inhibitors (PPIs) according to its indications, comorbidities and its related Pharmacoeconomics in a tertiary care teaching hospital, so as to effectively use the limited resources and if possible, significantly reduce the economic burden on the healthcare system.

Methods

This prospective observational study was carried out in a 1155 bedded tertiary care teaching hospital in Pune region. Institutional Ethics Committee approval 0321154-154 was obtained before commencement of the study. Data was collected prospectively from the indoor case files of 300 adult patients admitted from December 2021 to February 2022, who received IV PPI after admission. Pantoprazole was the only PPI available at the hospital during the study duration in IV (intravenous) formulation as well as oral. Data thus collected was analysed for patient demographic characteristics, comorbidities and indications for IV PPIs. Prescription of IV PPIs was studied for dose, frequency and duration. Other drugs administered concomitantly were studied for potential Drug-drug interactions (DDIs) with IV PPIs. Appropriateness of the IV PPI therapy was determined by using Stress ulcer prophylaxis guidelines (6).

Patients who were potential candidates for oral PPI therapy: Patients who were potential candidates that could be shifted from intravenous to oral PPI therapy was determined. Score of 1 was given for every YES answer. Small checklist was done and filled according to the case records of each patient which comprised of the 5 items:

- Was the patient not moribund? Y/N (Yes/No)
- Was the patient conscious? Y/N
- Was the patient non post operative? Y/N
- Were other drugs of oral formulation given? Y/N
- Was the patient tolerating oral feeds? Y/N

It was observed that patients who received a score of 4 or 5, were potential candidates that could be shifted from intravenous to oral PPI therapy. Moreover, percentage reduction in the cost of administration of PPI therapy in these potential candidates for oral PPI therapy was determined by the formula:- (7).

O: Observed price: Cost of administration of IV PPI therapy per patient

N: New price: Cost of administration of oral PPI therapy per patient $= \frac{O - N}{O} \times 100$

This highlighted the cost reduction that would have been possible per patient; had the potential candidates for oral PPI therapy been shifted to oral PPI therapy without affecting patient outcomes.

DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults which is 40 mg orally and parenterally for intravenous PPI Pantaprazole.

Monthly trend evaluation was performed for usage of intravenous PPIs by formula of DDD/100 bed days.

$$\text{DDD/100 bed days} = \frac{\text{No. of units administered in a given period} \times 100}{\text{DDD} \times \text{No of days} \times \text{No of beds} \times \text{Occupancy index}}$$

Anatomical therapeutic chemical (ATC) classification system code for IV proton pump inhibitor pantoprazole is A02BC02. Possible DDIs attributable to PPIs were anticipated by performing a systematic search of the MEDLINE database for English language articles with the keywords 'proton pump inhibitors' medical subject heading (MeSH) OR 'pantoprazole' (substance name) AND 'drug interactions' (MeSH) AND 'humans' (MeSH). The data thus found was correlated with the DDIs findings in the wards.

The study population comprised of all indoor patients above 18yrs of age who were prescribed PPIs while all patients below 18yrs of age were excluded. A study showed IV PPIs were prescribed in 68.5% of patients without any proper indication (8). Using this as prevalence, sample size was calculated as follows:

$$n = \frac{d \times d}{Z^2 \times P \times Q}$$

n – sample size

Z is confidence level (e.g., Z = 1.96 for 95% confidence)

P is prevalence 68.5% - 70%

Q= (1-P)

d is precision/error - 8%

Hence, Z = 1.96, P = 70%, Q = (1-P) = 30, d = 8%

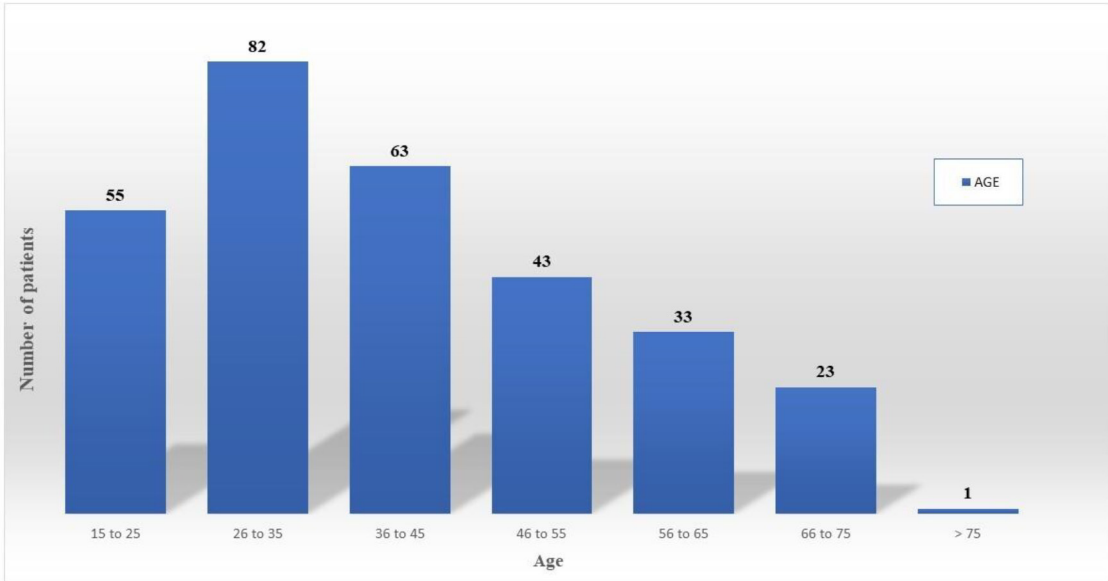
$$n = \frac{Z2 \times P \times Q}{d \times d} = \frac{(1.96)2 \times 70}{8 \times 8} \times \frac{30 = 8067}{64} = 292.32$$

Rounded off to 300 patient files.

Collected data was analysed using the Statistical Package for Microsoft Excel 2019 (Version 2204) for analysis of demographic parameters. Age is presented as mean (± S.D) whereas other demographic data is expressed as percentage of whole. Wilcoxon signed test on Social Science Statistics website was applied to find if there was a significant cost difference in parenteral and oral PPI therapies.

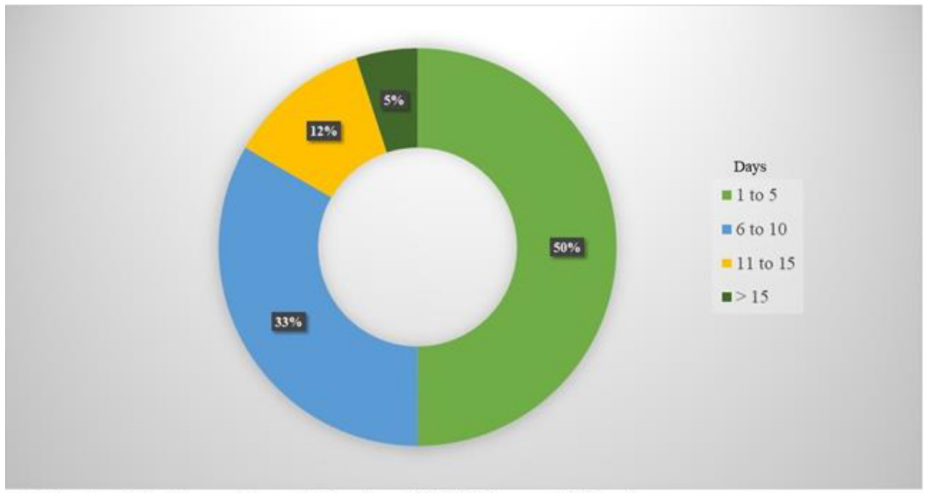
Results

The mean age of the study population was 41.18 yrs (S.D. ± 15.91 yrs). Most of the patients were in the age group of 26-35 yrs (27.33%), followed by 36 to 45 yrs (21%) (Figure 1). Out of 300 patients, 216 (72%) were males whereas 84 (28%) were females. The mean duration of PPI therapy of the study population was 6.9 (SD ± 6.12) days. A total 150 (50%) patients received IV PPI therapy for 1 to 5 days, while 100 patients (33%) received it for 6 to 10 days (Figure 2). Amongst the total patients studied-188 (63%) patients belonged to surgical wards and 112 (37%) belonged to non-surgical wards. Most of the patients receiving PPIs had Hypertension (47) 8.66%, 25 patients had diabetes mellitus while 16 had anaemia. Both diabetes and hypertension were found in 7 patients. A major chunk of 126 patients had diverse comorbidities like liver cirrhosis, acute kidney injury, dilated cardiomyopathy, eclampsia, etc. (Figure 3). It was observed that 192 (62.66%) patients were prescribed IV PPIs inappropriately for reasons other than those indicated for stress ulcer prophylaxis; while only 108 patients (37.33%) were prescribed PPIs appropriately for stress ulcer prophylaxis (6). (Figure 4). Other concomitant medications prescribed were antimicrobials 357 (36.06%), followed by antiemetic drugs 250 (25.25%), haematinics 79 (7.97%) and diuretics 79 (7.97%) (Figure 5).



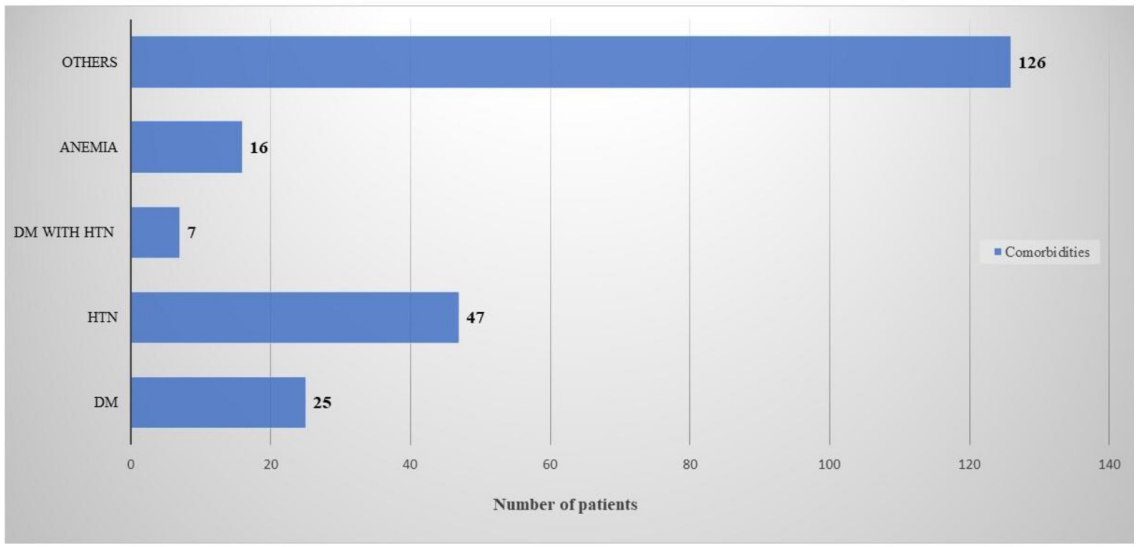
n:300 (number of patients)

Figure 1. Age-wise distribution of patients



n:300 (number of patients)

Figure 2. Duration of IV PPI Therapy (In Days)



n:300 (number of patients)

Figure 3. Comorbidities in patients on IV PPIs

When patients were evaluated as regards to potential candidates for oral PPI therapy-136 patients scored 4 and 87 scored 5, thus a total 223 (74%) patients were found to be potential candidates for oral PPI therapy (Figure 6). Potential DDIs with PPIs were enumerated performing a systematic search of the MEDLINE database (Table 1).

Table 1. Possible DDIs involving PPIs.

DDIs involving PPIs	Outcome of interaction	Number	Percentage
PPI + Clopidogrel	Increased effectiveness of clopidogrel	18	6
PPI + Amikacin	Hypomagnesia	2	0.66
PPI + Iron Sucrose	Decreases effect of iron sucrose	44	14.66
PPI + Vitcofol	Decreases levels of cyanocobalamin by inhibition of GI absorption	35	11.66
PPI + Digoxin	Increased effects of digoxin	9	0

Table 2. Cost of utilization of intravenous vs oral PPI therapy.

Intravenous	Price	Oral price
Pantoprazole formulation	10.38	1.36
100 ml NS	13.56	0
Needle	1.2	0
Syringe	3.2	0
Infusion set	12	0
Gloves	11	0
Intra Cath	6.5	0
Three-way	6.5	0
Total cost of PPI therapy per patient	64.34	1.36

DDD/100 bed days:

No of IV Pantoprazole units utilised from the drug store during study period of 90 days were – 29209 injections (DDD: 40, No. of days: 90, No. of beds: 1155, occupancy index: 0.8). Therefore, IV PPI utilisation was 0.87 DDD/100 bed days.

Cost of utilization of intravenous vs oral PPI therapy:

The cost of intravenous PPI therapy per patient (as per government supply rates) was found to be 64.34 INR and for oral PPI therapy was found to be a meagre 1.36 INR (Table 2). Thus, cost of intravenous therapy of 300 patients in study duration amounted to 1,33,312.48 INR while that oral therapy would have amounted to 2,817.92 INR. A difference of 1,30,494.56 INR in 300 patients for 90 days. Furthermore, percentage reduction in the cost of administration of PPI therapy per patient in the potential candidates for oral PPI therapy was determined and it was found to be 97.8% (7).

As per above checklist total 223 (74%) patients were found to be potential candidates for oral PPI therapy and taking in consideration the duration of IV PPI given to these patients -the mean cost of each intravenous PPI therapy was 444.38 INR and that for oral was 9.39 INR. Shifting the potential patients from IV PPI to oral formulation could have saved statistically significant amount of therapy cost without adverse clinical outcomes.

Wilcoxon signed test on Social Science Statistics website was applied to find if there can be a significant cost difference in parenteral and oral PPI therapies (9). The results of the test were found to be significant at Z statistics value of 17.32.

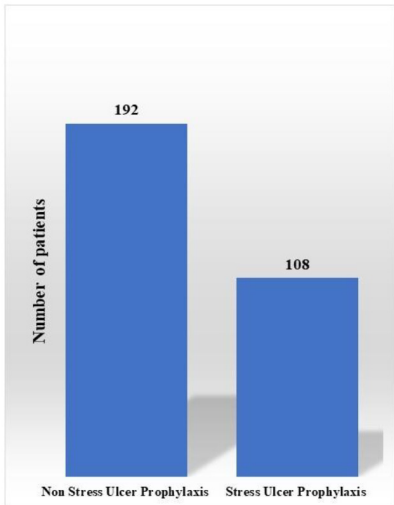


Figure 4. Indications for IV PPIs

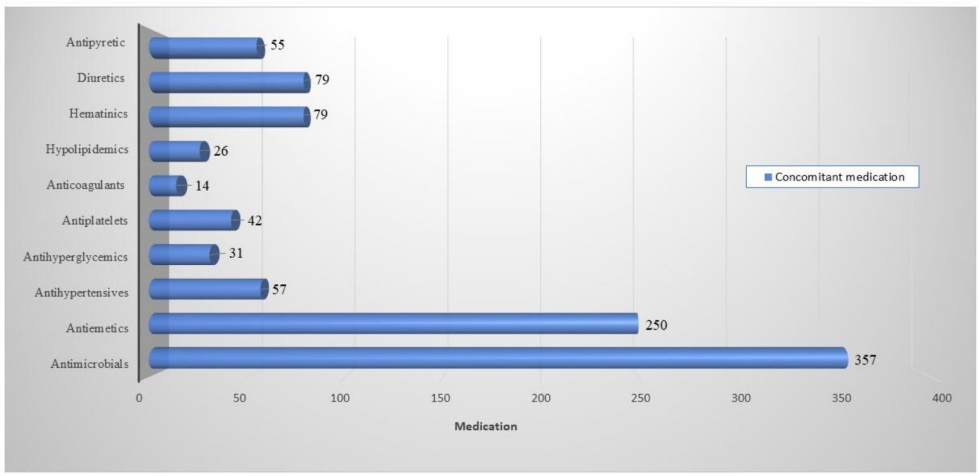


Figure 5. Concomitant medications with IV PPIs

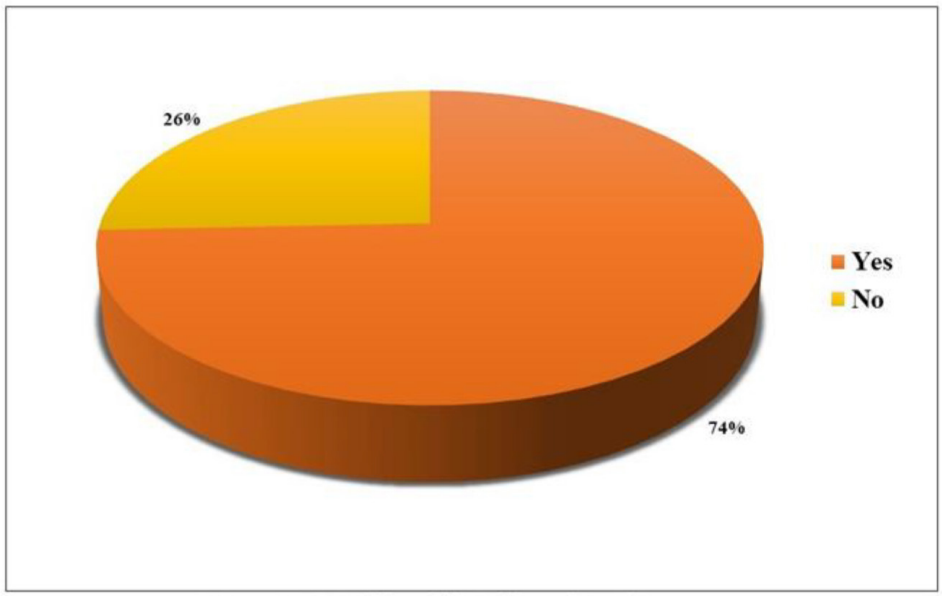


Figure 6. Potential candidates for oral PPI therapy

Discussion

World Health Organisation (WHO) has outlined rational use of medicines as "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." (10). Misuse of injectable formulations in patients who are potential candidates for oral formulations is also an aspect of inappropriate prescribing of drugs. Such prescribing policies result in wastage of scarce resources. Methods such as supervision, audit and feedback are advocated for promoting rational use of medications. Therefore, data of 300 random indoor patients receiving IV PPI was collected over 3 months and was analysed. It was observed that injection Pantaprazole was the only IV PPI used as it was the only available PPI on the hospital inventory. Earlier studies in emergency wards have also found injection Pantaprazole as the most commonly used PPI (11,12).

As per the demographic analysis of the study population the mean age was 41.18 years (SD± 15.91) which differs from other PPI studies; as those study populations comprised mostly of a decade older patient pool, possibly due to exclusion of pregnant females (13). The greater percentage of male patients than female patients is in agreement with other studies which reflects the higher admission rates of male patients to hospitals (12,13). The mean duration of intravenous PPI therapy was 6.9 days (SD± 6.12). There are similar studies, but in contrast to the duration of PPI therapy they have calculated the percentage of length of hospital stay and found it to be 1-10 days for 147 patients (86.5%) and their median length of hospital stay of the study population was 6.00± 4.03 (11).

The "Joint Trust Guideline for Use of Stress Ulcer Prophylaxis in Adult Critically Ill Patients" gives guidelines for effective use of PPI (6). Appropriateness evaluated accordingly suggested that only 108 patients (37.33%) were prescribed PPIs appropriately for Stress ulcer prophylaxis. These results were not in accordance to a study conducted in non-ICU hospitalized patients that showed (77.5%) prescriptions were for stress ulcer prophylaxis and were appropriate (4). On the contrary NICE guidelines were followed by one study and found that most of the patients (42.4%) were prescribed PPIs which was not in accordance to it whereas 27.6% patients were prescribed PPIs along with NSAIDs (11).

Polypharmacy as a norm was also seen in our study; wherein antimicrobials remained most commonly prescribed drugs (36.06%), followed by antiemetic drugs (25.25%). Another similar study shows that antimicrobials were mostly commonly prescribed concurrent medications (22.5%) (2,11). DDD/100 bed days is a standard tool used in indoor DUR. In this study utilisation for intravenous PPI was 0.87 DDD/100 bed days. Other studies show similar findings (0.929 DDD/100 bed days) (11).

As intravenous formulations are costlier than their oral counterparts, they have a considerable burden on the healthcare expenditure. Therefore, an effort was made to evaluate whether patients could be clinically shifted to oral PPI and astonishingly 223 out of the 300-sample size (74%) patients could be prescribed oral formulations.

Numerous studies have evaluated appropriateness of use of PPI, but have refrained to comment on the aspect of Pharmacoeconomics and the cost of administration of PPI therapy per patient. The cost of intravenous PPI therapy per patient per day was found to be 64.34 INR whereas the same for oral PPI therapy was found to be a meagre 1.36 INR. Similar studies showed that mean cost per day was high in patients prescribed with pantoprazole injection (43.38 ± 20.45) (2,11). Additionally, majority of the patients received IV pantaprazole twice daily whereas recommended dosing frequency is once per day and the duration of therapy was 6.9 (SD ± 6.12) days wherein 50 % of the patients received IV pantaprazole up to five days and remaining 50% more than 5 days.

Shifting patients from IV to oral formulations of PPIs and the resultant reduction in the cost of administration has not been studied extensively. Rationalising the use of IV Pantaprazole, while additionally shifting the potential patients from IV PPI to oral formulation could have a statistically significant but positive impact on the hospital pharmacoeconomics, especially in a resource limited setting of a tertiary care government hospital. On comparing the cost of administration of both IV and oral pantoprazole therapies, we found that shifting these potential oral candidates to oral PPI therapy will reduce the economic burden of PPI therapy by 97.8% per patient in the healthcare system.

The limitations of this study are: a random sample of 300 patients over 3 months was analysed. With adequate manpower and resources, larger study could be done and utilization of intravenous PPI over a whole year in all patients could be studied to understand the pharmaco-economics related to it. The cost of the manpower required for intravenous PPI therapy has not been taken into consideration.

In conclusion, the present study determined the total consumption of PPIs to be 0.87 DDD/100 bed days. Study findings suggest that around 223 of the 300 patients as per clinical status were deemed suitable for oral PPI therapy than parenteral. Such minor but important clinical revisions in therapy on daily rounds by the treating physicians, can not only contribute to rational pharmacotherapy, but also help curb the undue expenditures on the healthcare system in a government setup and also benefit by minimizing possible DDIs. Thus, rational pharmacotherapy is a team work where treating physician is the back-bone. The need of the hour is that all medical professionals work in unison for the effective use of PPIs by laying out specific guidelines for the same.

References

1. WHO. Introduction to drug utilization research / WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services. World Health Organization: Geneva, Switzerland. 2003;1–49.
2. Bahadori A, Peyrovi H, Ashghali-Farahani M, Hajibabaee F, Haghani H. The relationship between nursing leadership and patient satisfaction. Int J Med Res Heal Sci. 2016;5(10):134–41.
3. Machado-Alba J, Fernández A, Castrillón JD, et al. Prescribing patterns and economic costs of proton pump inhibitors in Colombia. Colomb Med. 2013;44(1):13–8.
4. Heidelbaugh JJ, Kim AH, Walker PC. Overutilization of proton-pump inhibitors: What the clinician needs to know. Therap Adv Gastroenterol. 2012;5(4):219–32.
5. Florentin M. Proton pump inhibitor-induced hypomagnesemia: A new challenge. World J Nephrol. 2012;1(6):151.
6. Madsen KR, Lorentzen K, Clausen N, Oberg E, Kirkegaard PR, Maymann-Holler N, Møller MH; Danish Society of Intensive Care Medicine; Danish Society of Anesthesiology and Intensive Care Medicine. Guideline for stress ulcer prophylaxis in the intensive care unit. Dan Med J. 2014 Mar;61(3):C4811.
7. Febrina D Permata and Wustari L Mangundjaya. The role of work engagement in the relationship of job autonomy and proactive work behavior for organizational sustainability 2021 IOP Conf. Ser.: Earth Environ. Sci. 716 012055.
8. Perwaiz M. Inappropriate use of intravenous PPI for Stress Ulcer Prophylaxis in an inner city community hospital. J Clin Med Res. 2010;2(5):215–9.
9. Sign test calculator. Available from: https://www.socscistatistics.com/tests/signtest/default.aspx
10. Promoting rational use of medicines World Health Organization. Available from: https://www.who.int/activities/promoting-rational-use-of-medicines
11. D'souza AM, Shastry CS, Mateti UV, Kabekkodu S, Chand S. Drug utilization and evaluation of proton pump inhibitors in general medicine ward of a tertiary care hospital. J Pharm Sci Res. 2019;11(6):2174–9.
12. Kaur S, Rajagopalan S, Kaur N, et al. Drug utilization study in medical emergency unit of a tertiary care hospital in north India. Emerg Med Int. 2014;2014:1–5.
13. Patil R, Aithal S, Hooli TV, HV V. Drug utilisation study of proton pumps inhibitors in inpatients of a tertiary care hospital: a cross-sectional study. Natl J Integr Res Med. 2015;6(5):62–5.