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Research article

Assessment of prescribing Pattern of proton Pump inhibitor and histamine 2 receptor antagonist

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Abstract

Proton Pump Inhibitors (PPIs) remain the leading evidence based therapy for upper Gastro intestinal disorders, including gastro-esophageal reflux disease, dyspepsia, peptic ulcer disease, NSAID-induced ulcer, eradication of Helicobacter pylori, and hyper secretory disorders. H2 receptor antagonists like ranitidine is the first choice H2 receptor antagonist in most patient. Our study aimed about the assessment of the prescribing pattern of PPIs and H2 receptor blockers. Our other objectives were to assess therapeutic appropriateness with standard guideline, ADR &Drug Interactions related to PPI &H2 receptor antagonist. Our study was a prospective observational study, included 209 patients, was conducted in a tertiary care Bangalore Baptist Hospital, Bangalore, INDIA for a period of six months. The results of this study observed that males were more using PPIs than females. Therapeutic appropriateness was mostly correct among both PPIs and H2 receptor blockers. We can conclude that continuous medical education with focus on rational drug use and evidence based medicine should form part of the program of the hospital. They should be involved in collection and presentation of prescribing data as part of clinical audit and also education of patients/caretakers. Also hospitals should consider developing controlled policies like formulary restriction, stop orders for specific indications, and automatic switch-order to oral PPI if patient is receiving oral feeding. This study could provide direction for much needed randomized controlled trials evaluating the use of PPIs in the first year of life, including specific recommended dosing, duration of therapy, and effectiveness of treatment.

Key words: PPI, Appropriateness Use, H2 Receptor Antagonist, Gender.

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1. Introduction

H2–receptor antagonists like Ranitidine ,which is the first-choice H2–receptor antagonist in most patients, has fewer side effects than cimetidine and is less likely to cause interactions with renal or hepatic impairment, concurrent multiple therapy and those on high doses for hypersecratory states. Ranitidine is the

recommended injectable H2-receptor antagonist. Cimetidine is effective in treating gastric and duodenal ulcers and will also relieve peptic esophagitis. It inhibits drug metabolism and so should be avoided in patients stabilized on Warfarin, Phenytoin, Theophylline and Aminophylline [1].

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 [2].

Following an initial short healing course of full dose PPI, the majority of patients can stop treatment or should be maintained on the lowest possible dose to control symptoms or taken on demand in response to symptoms. Maintenance therapy with PPIs may be indicated for patients with complications of reflux disease such as erosive ulceration, structuring esophagitis, Barrett's esophagus, Zollinger-Ellison syndrome and largyngopharyngeal reflux or in the prophylaxis of NSAIDs induced peptic ulceration and may require longer treatment with full or high dose PPI.[3]

PPIs are generally well tolerated. The most common adverse reactions seen in adults are flatulence, headache, diarrhea, nausea, abdominal pain, and vomiting. The use of PPIs has also been associated with drug interactions, fractures, hypomagnesemia, and Clostridium difficile-associated diarrhea (CDAD). Clinically significant drug interactions with PPIs are rare. Chronic acid suppression can minimize the effectiveness of any medication requiring an acidic environment for absorption. Commonly prescribed medications affected by acid suppression are ampicillin esters, digoxin, atazanavir, ketoconazole, and iron salts.

There is also risk of drug interactions between PPIs and other medications that are metabolized via the cytochrome P450 system. While specific interactions are not well documented, there is substantial evidence regarding an interaction between clopidogrel and omeprazole [4].

2. Materials and Methods

Study design

This study is a hospital based prospective and observational study conducted Bangalore Baptist Hospital, Bangalore, India, a 500 bedded multi-specialty tertiary care teaching hospital. (October 2015 to March 2016)

Study population

The study was conducted in the Department of Surgery ward, Medicine ward, ICU, CCU Bangalore Baptist Hospital, Bangalore, India

Sampling method

The study method involves selection of patients based on the inclusion and exclusion criteria.

Inclusion Criteria

All patients admitted to the Surgery ward, Medicine ward, ICU, CCU only adults of either sex including Pregnant/lactating mothers were taken.

Exclusion Criteria

- All pediatric patients
- Outpatient Department

Patient Data Collection Form

The first step in the study was to design a Data collection form (annexure 1). The patient data collection form was used to

collect all the details like Inpatients number, Patient name, Age, Sex, Date of admission, Date of discharge, Chief complaints (c/o), History of Present Illness (HOPI), Past Medication history, Laboratory data, Culture sensitivity test, Diagnosis and Therapeutic management.

Study procedure

The patient demographics and all medically relevant information will be noted in a predefined data collection form. Alternatively, these case charts will be reviewed for prescription legibility and completeness, unaccepted abbreviations, capture of relevant information in case sheet, contraindication, drug interactions and adverse drug events and dose calculations based on their weight and BSA . The changes and the daily notes in the case sheets will be followed until the patient is discharged or shift to other wards. The prescription guidelines, Micromedex, Medscape and references books will be used as tools to review the prescription and case charts. The data will be stored confidentially and will be subjected to further analysis using appropriate software.

Prescription Analysis

The second step in the study is prescription analysis. It was used to study various parameters like prescribing pattern, Drug to Drug interaction, Adverse Drug Events (ADEs), Adverse Drug Reactions.

3. Results and discussion

Results

Age Categorization

The study includes 209 patients and out of them most of the patients was observed from the age group between 70 – 79 years old (17.22%) and next from the age group 10 – 19 years (16.74%) follows with 50 – 59 years (15.78%).

Table 1. Age Categorization

Age (years)	Number of Patients (n=209)	Percentage (%)
10-19	35	16.74
20-29	30	14.35
30-39	28	13.39
40-49	21	10.04
50-59	33	15.78
60-69	26	12.44
70-79	36	17.22

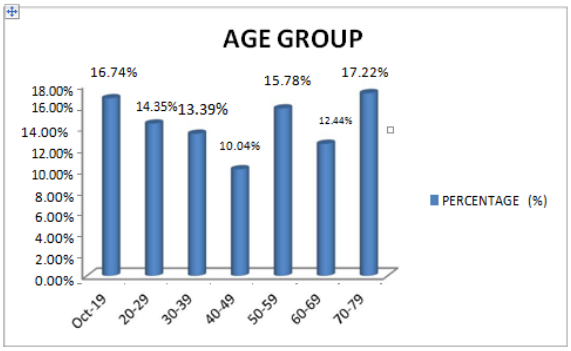

Figure 1. Age Group

Gender Wise Distribution

Out of 209 patients, 137 patients (65.55%) were male and 72 patients (34.44%) belong to female gender.

Table 2. Gender Wise Distribution

Gender	Number of patients (n=209)	Percentage (%)
Male	137	65.55
Female	72	34.44

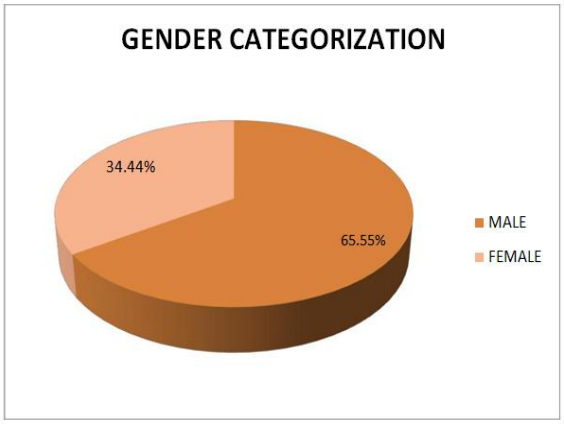

Figure 2. Gender Categorization

Length of Hospital Stay

Out of 209 patients, most of the patients were stayed in the hospital 2-4 days (51.19%) followed by 5 - 7 days (30.62%) and 12 -15 days. (Table 3 and figure 3).

Table 3. Length of Hospital Stay

Stay (days)	Number (n=209)	Percentage (%)
2– 4	107	51.19
5– 7	64	30.62
8– 11	28	1.39
12 – 15	8	3.84
16 – 19	2	0.96

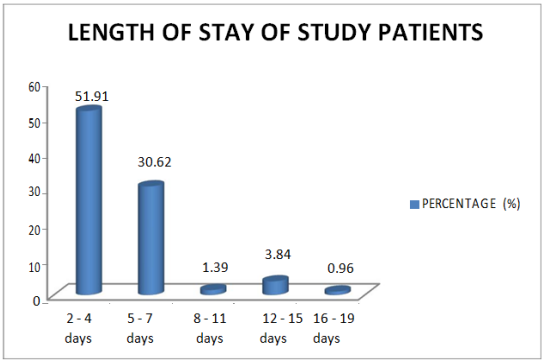

Figure 3. Length of Stay of Study Patient

Diagnosis

Most of the patients were diagnosed as gastro esophageal reflux disease with 31.2% (65 patients) followed by diabetes mellitus and hypertension (38 patients, 18.18%) and pain from gas with 15.7% (33 patients) (Table 4).

Table 4. Diagnosis

Diagnosis	No. of Patients	Percentage (%)
GERD	65	31.2
Pain from gas	33	15.7
Esophagitis	21	10.04
Bronchitis	6	2.87
Viral hepatitis	9	4.32
Thrombocytopenia	11	5.26
COPD	26	12.44
DM/HTN	38	18.18

No. of Medicines per Prescription

Out of 209 patients, 126 patients were prescribed with 4 – 7 medicines (60.28%) per prescription followed by 3 medicines (31.57%) per prescription and >7 (8.13%) no. of medicines per prescription.

Table 5. No. of Medicines Per Prescription

No. of medicines	Number of patients (n=209)		Total	Percentage (%)
	Male	Female		
0 – 3	35	31	66	31.57
4 -7	75	51	126	60.28
>7	11	6	17	8.13

Prescribing Pattern of PPI

Among 209 patients, omeprazole (46.89%) were the highly prescribed followed by pantoprazole (34.4%) and then rabeprazole (29.62%).

Table 6. Prescribing Pattern of PPI

PPIs		Number of patients		Percentage (%)
		M	F	
Omeprazole	INJ	17	16	46.89
	CAP	39	26	
Pantoprazole	INJ	13	14	34.4
	CAP	26	19	
Rabeprazole	CAP	21	18	29.62

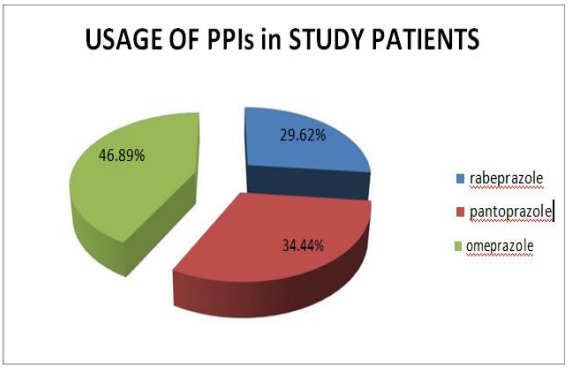

Figure 4. Usage of PPIs in study patients

Prescribing Pattern of H2 Blockers

Under H2 blockers class of drugs, Ranitidine was prescribed to 51 patients (24.41%)

Table 7. Prescribing Pattern of H2 Blockers

H2 Blockers		Number of patients		Percentage (%)
		Male	Female	
Ranitidine	INJ	12	7	24.14
	CAP	16	16	

Commonly Used Concurrent Medications of PPI

Among 209 patients, the commonly used medications with PPIs are metformin (31.16%) followed by insulin (29.65%), glipizide (18.18%) enoxaparin ((17.75%), amoxicillin and potassium clavunate, ondansetron (17.22%) and pipperacillin (16.75%).

Table 8. Commonly Used Concurrent Medications of PPI

Drugs	No. of Patients	Percentage (%)
Paracetomol	21	10.16
Gabapentin	32	15.31
Metformin	65	31.16
Shelcal	34	16.26
Clinidipine	32	15.32
Pipperacillin	35	16.75
Insulin	62	29.65
Augmentin	36	17.22
Ondansetron	36	17.22
Enoxaparin	37	17.75
Glipizide	38	18.18

Commonly Used Concurrent Medications of H2 Blockers

Among 209 patients, the commonly used medications with H2 blockers are atenolol (76.5%) followed by diclofenac (43.2%), insulin, ondansetron (41.9%) and paracetomol, domperidone (39.5%).

Table 9. Commonly Used Concurrent Medications of H2 Blockers

Drugs	No. of Patients	Percentage (%)
Diclofenac	35	43.2
Atenolol	62	76.5
Paracetomol	32	39.5
Insulin	34	41.9
Flucanazole	25	30.85
Domperidone	32	39.5
Ondansetron	34	41.9
Tramadol	26	32.08
Atorvastatin	25	30.85

Appropriateness of PPI

Based on 5 parameters and criteria, a medicine or medicine combination could have a score of minimum 0 to a maximum of 10 in the appropriateness scale. After assigning score to each medicine of a prescription with either 0 (inappropriate) or 2 (most appropriate), an average score of appropriateness for medicines in a prescription was obtained by dividing the total score of all medicines by number of medicines in that particular prescription. Then, the prescriptions were allotted to following 3 categories

Appropriateness of H2 Blockers

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Table 10. Drug Interactions in The Prescriptions

Drug	Interacting drug	Effect	Suggestion	Severity
Omeprazole	Glipizide	CYP2C9 Inhibitors decrease the metabolism of CYP2C9 Substrates	Monitor for increased effects of the CYP substrate if a CYP inhibitor is initiated/dose increased, and decreased effects if a CYP inhibitor is discontinued/dose decreased	Major
	Clopidogrel	Omeprazole may diminish the antiplatelet effect of Clopidogrel. Omeprazole may decrease serum concentrations of the active metabolite(s) of Clopidogrel	Clopidogrel prescribing information recommends avoiding concurrent use with omeprazole due to possibility that combined use may result in decrease clopidogrel effectiveness	Major
	Atorvastatin	Proton Pump Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors	Monitor for evidence of rhabdomyolysis and other adverse effects if a proton pump inhibitor and an HMG-CoA reductase inhibitor are coadministered.	Major
Ranitidine	Atorvastatin	P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of P-glycoprotein/ABCB1 Substrates.	Monitor for increased effects of P-glycoprotein (Pgp) substrates if a Pgp inhibitor is started or if the dose of a concurrently used Pgp inhibitor is increased. Conversely, monitor for decreased substrate effects/toxicity if a Pgp inhibitor is discontinued or if the dose of concurrently used Pgp inhibitor is decreased.	Moderate

Table 11. Appropriateness of PPI

Prescription	Number of prescriptions (n=206)	Percentage (%)
Most appropriate	109	52.91
Appropriate	97	47.08
Inappropriate	-	-

Table 12. Appropriateness Of H2 Blockers

Prescription	Number of prescriptions (n=206)	Percentage (%)	Prescription
Most appropriate	112	54.36	Most appropriate
Appropriate	94	44.97	Appropriate
Inappropriate	-	-	Inappropriate

Discussion

Although the use of PPIs has increased significantly over a period of time in Europe and North America, this study shows that the overall use of PPIs (*e.g*., pantoprazole), is higher than that of H2RAs (such as ranitidine) at least among our patients. A majority (17%) of patients studied was aged 70 years and above, a situation similar to what had been published by Carvajal *et al.* in 2004 in Spain [5]. The proportion of elderly patients was higher in this study because they harbor serious co-morbid illnesses that bring them to the hospital and require admission for longer periods. A study conducted for over one year in a single county hospital in the USA showed that only 22.5% of all outpatient prescriptions of pantoprazole had a proper indication. A recent study revealed that 22% of hospitalized patients had received SUP in a non ICU setting, out of which 54% were discharged and given ASDs without proper indication, which had cost the hospital $111,791 annually.

Similarly, studies published in Europe and Ireland showed that 51% and 57% of their patients respectively, were given PPIs improperly. Maclaren *et al.* had illustrated in their study that even after implementation of intravenous PPI guidelines, prescribing practices for SUP did not show any improvement. Most of the patients were on PPI (omeprazole). This is comparable to what had been reported by Daley *et al.* in their study where 63.9% of ICU clinicians chose an H2RA as their first-line drug while 23% chose PPIs, when asked for their preferred choice between H2RAs and PPIs. From the clinicians who chose PPIs, about 64.7% used them when H2RAs failed initially. The frequency of prescribing pantoprazole was found to be higher in patients with an existing risk factor and was mostly recommended by physicians. Cardiologists from the medical department issued the most prescriptions, followed by neurologists. The reason was that they had the highest number of patients, most of them elderly who were on aspirin or anticoagulants for either stroke prevention or cardiac ischemia[6].

In the surgery department, most prescriptions were issued by orthopedic surgeons, followed by general surgeons. Their patients had major surgeries and were either on NSAIDs for pain management, anticoagulants for deep vein thrombosis prophylaxis or on both drugs. Our study reveals that there is significant evidence that ASDs are not being misused. Individual hospitals should develop their own strategies to overcome such misuse, notably for PPIs. Strategies that can be used include controlled policies like formulary restriction, PPI order sheets or stop-orders for specific indications. This practice has been successfully implemented in reducing antibiotic misuse. The other strategy of immediate concurrent feedback, which involves providing instant feedback to doctors at the time of prescription, was deemed to be improper. However, a study showed that this approach was associated with more rational prescribing of ASDs and was important in saving resources. Our results demonstrate that PPIs appear to be associated with elevated risk of MI in the

general population; and H2 blockers show no such association. The associations are independent of clopidogrel use or age-related risks and are seen in two large independent datasets and a prospective cohort. In particular, the association is seen outside of the high-risk populations previously examined, such as the elderly or patients with ACS [7].

The current study suggests that the risk of PPIs may extend beyond previously studied high risk individuals. These findings confirm and extend the findings of Shih and colleagues, which suggested that PPIs were associated with short term cardiovascular harm amongst Taiwanese individuals, and are consistent with studies which have shown that PPIs may diminish the cardioprotective effects of drugs that do not depend on CYP2C19 activation, such as ticagrelor [8].

Writing and implementing guidelines for the uses of ASDs, mainly PPIs, by pharmacists can be another strategy to reduce misuse. The study published by Skledar *et al.* showed pharmacists and physicians collaboratively developed evidence-based practice guidelines and adherence to it produced a 50% improvement in correct intravenous pantoprazole use. Such a practice guideline can be in the form of a verbal, written or electronic communication. Our study is subject to several limitations. Most importantly, these observational data may be subject to confounding in multiple ways, and it is possible that PPI usage is merely a marker of a sicker patient population. For example, we were unable to control for factors such as obesity and insulin resistance, and it may be that in some individuals PPIs were prescribed for angina that was misidentified as acid reflux. However, the observation that alternative heartburn medications such as H2 blockers were not associated with harm lends support to the concept that PPIs may specifically promote risk. Although this study did not evaluate the clinical outcomes and safety of the PPIs, it could provide direction for much needed randomized controlled trials evaluating the use of PPIs in the first year of life, including specific recommended dosing, duration of therapy, and effectiveness of treatment

Conclusion

PPI prescribing without documented valid indications is highly prevalent in our practice. Approaches to tackle this medication safety issue could include documented physician review of PPI indications at each patient contact. We further recommend interventions such as pharmacist advice being documented in electronic medication records, and flagging medications that lack appropriate indications. Continuous medical education with focus on rational drug use and evidence based medicine should form part of the program of the hospital. They should be involved in collection and presentation of prescribing data as part of clinical audit ad also education of patients/caretakers.. Also hospitals should consider developing controlled policies like formulary restriction, stop-orders for specific indications, and automatic switch-order to oral PPI if patient is receiving oral feeding. Educating physicians and surgeons through newsletter and electronic email alert detailing appropriate indications (evidenced-base) of IV PPI can also reduce the misuses of IV PPI. PPI can constitute a type of policy in its own right, with its own frameworks and innovation-related goals and even its own specialized agencies. However, PPI can also be understood as a policy instrument that seeks to uplift the capabilities within procuring bodies, and improve the framework conditions to enable the general public procurement practice to ask for and buy more

innovations. High-dose, chronic PPI use is prevalent, despite a high degree of co-morbidity in the target population and significant treatment failures. There are opportunities for substantial cost savings in relation to PPI prescribing if implementation of clinical guidelines in terms of generic substitution and step-down therapy is implemented on a national basis.

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