Research Article

# Prospective Assessment of Prescribing Pattern of Intravenous Proton Pump Inhibitors in an Indian Tertiary-Care Teaching Hospital

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## ABSTRACT

**Context:** Inappropriate use of intravenous proton pump inhibitors (IV PPIs) has been a major challenge for private health-care setups. Inappropriate prescribing may result in increased shortages of IV PPIs in hospitals, therapeutic burden, adverse effects, and treatment costs. Therefore, the study was sought to determine drug utilization patterns (appropriateness and inappropriateness) of IV PPIs in an Indian tertiary-care teaching hospital. **Aims:** To assess the drug utilization pattern of IV PPIs in a tertiary-care teaching hospital. **Settings and Design:** This was a prospective observational study. **Methods and Material:** This study was conducted over a period of one month. Patients who were ≥18 years of age, who were admitted in the internal medicine, surgery, or gastroenterology wards, and who were receiving IV PPIs were included in the study. Paediatric patients and outpatients were not enrolled in the study. Ddemographics, past medication and surgery, current medical condition and medication, dose, dosing interval, duration of therapy, length of stay, and endoscopic details of each patient was collected from patients' case notes, treatment charts, and laboratory/diagnostic test reports, and evaluated for appropriateness regarding indication. **Statistical analysis:** Chi square test ($\chi^2$) was used to analyze the data. **Results:** Prospective assessment involved 611 patients over a 1-month period. For prophylaxis (stress ulcer, pre-operative and post-operative prophylaxis) and treatment, IV PPIs were prescribed inappropriately to 289 (89.2%) internal medicine and 97 (34.04%) surgery ward patients. Prolonged therapy was found in patients who received IV PPIs for stress ulcer prophylaxis. **Conclusion:** This study revealed significant inappropriateness of PPI administration with particular reference to indication to use, duration of therapy, and changeover of therapy in an Indian tertiary-care teaching hospital.

**Key words:** Intravenous proton pump inhibitors, Prescribing pattern, Prospective assessment, Rational drug use, Drug utilization evaluation.

## INTRODUCTION

Proton pump inhibitors (PPIs) have replaced histamine-2 receptor antagonists ($H_2$-RAs) worldwide for the treatment of gastro esophageal reflux disease (GERD) and peptic ulcer disease (PUD), maintenance therapy for GERD or hypersecretory states, and prevention of ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs).[1] However, oral PPIs may be inadequate to obtain desired therapeutic outcomes in the treatment of acid-related disorders (e.g., in cases of non-variceal upper gastrointestinal bleeding (UGB), Zollinger-Ellison Syndrome).[2] In order to obtain better treatment efficacy, physicians generally prescribe parenteral PPIs in place of oral PPIs or oral $H_2$-Ras.[2] However, inappropriate use of PPIs has been observed in numerous hospitals worldwide.[3,4] An increase in the prevalence of pneumonia and Campylobacter enteritis, risk of hip fracture and infection with Clostridium difficile, and acute interstitial nephritis and osteoporosis have been reported as consequences of long-term treatment with PPIs.[4-6] Furthermore, parenteral PPIs are relatively expensive, and

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inappropriate use can increase the treatment cost significantly for patients, especially in developing countries.[7] Achieving appropriateprescribing practices regarding parenteral PPIs will be necessary to obviate these issues and challenges.

Numerous methods have been used to evaluate patterns of drug use in hospitals, including prescription and physician surveys, analysis of drug sales or drug consumption data, and reviews of medical records.[7] Among these methods, prescription surveys have been the most popular for evaluating prescribing practices or medication use in hospitals. Such surveys are quick and inexpensive, and do not require the participation of prescribers or patients.[7] Health-care in India is highly privatized and poorly regulated.[8] IV PPIs are widely prescribed in hospitals. Prescribing patterns of IV PPIs have not been assessed so far. Therefore, we sought to determine the appropriateness and inappropriateness of IV PPIs use with particular reference to indication, dose, dosing interval and duration of therapy, and changeover of therapy (from an IV PPI to an oral PPI or $H_2$-RA) by a prospective survey in an Indian tertiary-care teaching hospital.

## MATERIALS AND METHODS

The study was conducted in a major tertiary-care teaching hospital in India. The hospital is a 1200-bed medical teaching hospital providing primary and specialized health care facilities to people of surrounding area. This hospital has about 20-30 patient admissions per day in internal medicine, 20-30 in surgery, and 1-2 in gastroenterology wards. This study was conducted over a period of one month. The Institutional Human Ethics Committee approval was obtained prior to the initiation of the study. Patients who were ≥18 years of age, who were admitted in the internal medicine, surgery, or gastroenterology wards, and who were receiving IV PPIs were included in the study. Paediatric patients and outpatients were not enrolled in the study. Demographics, past medication and surgery, current medical condition and medication, dose, duration of therapy, length of stay, and endoscopic details of each patient was collected by two clinical pharmacists from the following sources: *a*) patients' case notes, *b*) treatment charts, *c*) laboratory/diagnostic tests reports, *d*) interviews with the patients or the patients' care takers, and *e*) interviews with health-care professionals. Appropriate and inappropriate indications for use of IV PPIs (Table 1) were adopted from published standard guidelines[9,10] and independent decisions on prescribing patterns (appropriate or inappropriate) were made by the clinical pharmacists. There was no difference in judgment between the two clinical pharmacists. There was also no overestimation and underestimation of prescribing patterns. The appropriateness of changeover of therapy from an IV PPI to an oral PPI or $H_2$-RA was assessed on the basis of reasons (e.g., bleeding stopped, no high risk of ulcer found at endoscopy, resumption of oral intake, risk factor for stress ulcer resolved, absence of a specific reason, or therapy not changed) stated by prescribers. Total expenditure for IV PPIs and average cost/patient were calculated by considering the cost of IV PPIs/vial and duration (days) of treatment. Statistical analysis was performed using SPSS version 17.0. A chi-square test was used to compare rates of appropriate and inappropriate use of IVPPIs.

## RESULTS

The study population consisted of 611 patients (361 males, 250 females) and their mean age was 45.38 years

**Table 1: Appropriate and inappropriate indications for the use of intravenous proton pump inhibitors [9,10]**

| Appropriate indications | Inappropriate indications |
|---|---|
| Patients who are unconscious with any type of gastrointestinal ulcers erosive GERD | Nausea/vomiting<br>Stress ulcer prophylaxis not meeting appropriate criteria |
| Patients who are not able to tolerate oral drugs. | Suspected esophageal variceal bleed |
| Non variceal upper gastrointestinal bleed (UGIB)/Bleeding peptic ulcer. | Suspected gastritis |
| Prophylaxis of stress ulceration.<br>Mechanical ventilation ≥ 48 h<br>Coagulopathy (platelet count\50 K or INR (1.5)) | Lower Gastrointestinal bleed |
| Prevent acid aspiration syndrome during induction of surgical anaesthesia. | Previous History of acid peptic disease |
| Preoperative prophylaxis | Patients who are having esophagitis and are not fasting |
| Postoperative prophylaxis (on NPO status) | No indication stated and also patients are not fasting |
| Hypersecretory condition, Zollinger-Ellison Syndrome. | No indication stated but patients are fasting (receiving oral medications) |

NPO: Nil per os; UGIB: upper gastrointestinal bleed; GERD: gastro esophagus reflux disease; IV PPIs: Intravenous proton pump inhibitors

(S.D. = ± 17.23 years) of the 611 patients, 324 were from internal medicine, 285 from surgery, and 2 from gastroenterology wards. Very few patients had either upper gastrointestinal bleed (UGIB) or lower gastrointestinal bleed (LGIB) clinical condition at the time of admission. A majority of patients in internal medicine wards who received IV PPIs had other health condition including acute coronary symptoms, cerebrovascular accident, myocardial infarction, leptospira infection, dengue fever, acute gastroenteritis, acute febrile illness, asthma, chronic obstructive lung disease, poisoning due to snake bite, and drug consumption. A majority of patients who received IV PPIs in surgery wards had undergone operation for abscess, appendicitis, anal fistula, hernia, varicose vein, cholelithiasis, intestinal obstruction, colonic obstruction, carcinoma, cellulites, diabetic foot ulcer, gangrene, hemorrhoids, and peritonitis.

To understand further, patients were categorized by their symptoms considered or the reasons stated in the case notes to initiate IV PPI therapy. A majority of patients (550, 90.03%) received IV PPIs for stress ulcer, preoperative and postoperative prophylaxis. Only 43 (7.03%) patients received PPIs as treatment. The highest inappropriate indications to use IV PPIs were observed in the internal medicine ward, followed by surgery and then gastroenterology wards (Table 2). For stress ulcer prophylaxis, IV PPIs were prescribed inappropriately to a significantly higher number of patients both in internal medicine ($p< 0.05$; OR, 3.43; 95% CI, 1.54-7.63) and surgery ($p< 0.05$; OR, 10.82; 95% CI, 5.20-22.5) wards, thereby indicating a common cause for misuse of IV PPIs in an Indian tertiary-care hospital.

Endoscopy is an important diagnostic tool to identify gastrointestinal disorders. Hence, in most cases (variceal bleeding is an exception), an endoscopic test is required before initiating IV PPI therapy. Initiation of acid-suppression therapy prior to endoscopy may reduce the diagnostic yield of endoscopy. The observed time to endoscopy and endoscopic findings are given in Table 3. During our study, 29 patients underwent endoscopy after starting an IV PPI therapy (8 patients after < 1 day, 16 patients after 1 day, 4 patients after 2 days, and 1 patient after 3 days of IV PPI therapy) of the 29 patients, UGIB, LGIB and GERD were found in 5, 11, and 3 patients, respectively. Though the remaining 10 patients did not have a high risk for ulcer, bleeding or stigma, and showed normal study, they were continued on IV PPIs. The cost of performing endoscopy in this hospital is Rs. 1250 (~ $ 25).

Prescribed doses and dosing intervals for IV pantoprazole and rabeprazole were satisfactory in 100% of cases (Table 3). The prescribed dose of IV pantoprazole was a 40 mg IV bolus or a 40 mg IV infusion or an 80

**Table 2: Evaluation of appropriate and inappropriate use of intravenous pantoprazole and rabeprazole (IV PPIs) therapy in internal medicine and surgery wards of an Indian tertiary-care teaching hospital[a]**

| Indications | Appropriately or Inappropriately indicated patients (n (%)) | | | | | |
|---|---|---|---|---|---|---|
| | Internal medicine ward | | | Surgery ward | | |
| | Appropriate | Inappropriate | Total | Appropriate | Inappropriate | Total |
| **Stress ulcer prophylaxis** | 24 (7.14) | 255 (78.7) | 279 (86.11) | 11 (3.86) | 39 (13.68) | 50 (17.54) |
| **Post-operative prophylaxis** | 2 (0.62) | 00 | 2 (0.62) | 102 (35.79) | 2 (0.70) | 104 (36.49) |
| **Pre-operative prophylaxis** | 2 (0.62) | 00 | 2 (0.62) | 67 (23.51) | 46 (16.14) | 113 (39.65) |
| **Treatment** | | | | | | |
| **UGIB** | 01 (0.31) | 00 | 01 (0.31) | 03 (1.05) | 00 | 03 (1.05) |
| **LGIB** | 00 | 03 (0.92) | 03 (0.92) | 00 | 08 (2.81) | 08 (2.81) |
| **GERD** | 03 (0.92) | 00 | 03 (0.92) | 00 | 00 | 00 |
| **Previous history of acid peptic disease** | 00 | 06 (1.85) | 06 (1.85) | 00 | 00 | 00 |
| **Suspected esophageal variceal bleed** | 00 | 03 (0.92) | 03 (0.92) | 00 | 01 (0.35) | 01 (0.35) |
| **Suspected gastritis** | 00 | 08 (2.49) | 08 (2.49) | 00 | 00 | 00 |
| **Oesophagitis** | 01 (0.31) | 02 (0.61) | 03 (0.92) | 02 (0.70) | 00 | 02 (0.70) |
| **Prophylaxis and treatment*** | 2 (0.62) | 12 (3.7) | 14 (4.32) | 3 (1.05) | 1 (0.35) | 4 (1.41) |
| **Total** | 35 (10.8) | 289 (89.2) | 324 (100) | 188 (65.96) | 97 (34.04) | 285 (100) |

UGIB: upper gastrointestinal bleed; GERD: gastroesophageal reflux disease.

*Patients received IV PPI therapy for prophylaxis which was continued as treatment for known gastrointestinal diseases (oesophagitis = 5 patients; previous history of acid peptic disease = 9 patients; suspected gastritis = 4 patients).

[a]This Table does not include data on gastroenterology ward patients. Only two patients were admitted in the gastroenterology ward and we observed 50% appropriate (UGIB) and inappropriate (previous history of acid peptic disease) indications in this ward.

**Table 3: Intravenous proton pump inhibitors use characteristics in internal medicine and surgery wards**

| Characteristic | Patients (n (%) or Mean ± SD or days) | |
|---|---|---|
| | Internal medicine ward | Surgery ward |
| **NPO status (%)** | [n=324] | [n=285] |
| **Yes** | 31 (9.6) | 185 (64.9) |
| **No** | 293 (90.4) | 100 (35.1) |
| **Pantoprazole dose (%)** | [n=273] | [n=195] |
| **40 mg IV once daily** | 267 (97.80) | 191 (97.95) |
| **40 mg IV twice daily** | 6 (2.20) | 4 (2.05) |
| **40 mg IV bolus** | 258 (94.51) | 195 (100) |
| **40 mg IV infusion** | 13 (4.76) | - |
| **80 mg IV infusion** | 2 (0.73) | - |
| **Duration of use of IV pantoprazole (days)** | | |
| **Range** | 1-11 | 1-28 |
| **Mean ± SD** | 4.96 ± 2.86 | 8.98 ± 6.53 |
| **Rabeprazole dose (%)** | [n=46] | [n=85] |
| **20 mg IV once daily** | 46 (100) | 77 (90.59) |
| **20 mg IV twice daily** | - | 8 (9.41) |
| **20 mg IV bolus** | 46 (100) | 85 (100) |
| **Duration of use of IV rabeprazole (days)** | | |
| **Range** | 1-15 | 1-28 |
| **Mean ± SD** | 5.6 ± 4.30 | 9.26 ± 6.04 |
| **Pantoprazole (P) + Rabeprazole (R) dose (%)** | [n=5] | [n=5] |
| **40 mg IV once daily (P) + 20 mg IV once daily (R)** | 5 (100) | 5 (100) |
| **40 mg IV bolus (P) + 20 mg IV bolus (R)** | 5 (100) | 5 (100) |
| **Duration of use of IV P + R** | | |
| **Range** | 1-3 (P) + 1-6 (R) | 1-17 (P) + 2-10 (R) |
| **Mean ± SD** | 2 ± 1 (P) + 3.4 ± 2.07 (R) | 7.2 ± 6.42 (P) + 4.8 ± 3.35 R) |
| **Time to endoscopy (%)** | [n=324] | [n=285] |
| **Before starting IV PPI** | 0 | 0 |
| **< 1dayafter starting IV PPI** | 4 (1.2) | 4 (1.4) |
| **1 day after starting IV PPI** | 10 (3.1) | 6 (2.1) |
| **2 day after starting IV PPI*** | 1 (0.3) | 2 (0.7) |
| **3 day after starting IV PPI** | 1 (0.3) | 0 (0) |
| **Not performed** | 308 (95.1) | 273 (95.8) |
| **Endoscopic findings (%) n=28*** | [n=16] | [n=12] |
| **UGIB** | 1 (0.3) | 3 (1.0) |
| **LGIB** | 3 (0.9) | 8 (2.8) |
| **GERD** | 3 (0.9) | 0 (0) |
| **Normal study** | 9 (2.9) | 1 (0.4) |

NPO: Nil per os; GERD: gastro esophagus reflux disease; IV: intravenous; SD: standard deviation, IV PPIs: Intravenous proton pump inhibitors; *1 patient of UGIB from gastroenterology ward was not included

mg IV bolus followed by an 8 mg/h infusion. The prescribed IV bolus dose of rabeprazole was 20 mg. The duration of IV PPIs therapy in internal medicine and surgery wards are given in Table 3. Duration of IV PPIs therapy for stress ulcer prophylaxis in internal medicine and surgery wards patients was 1-11 (average duration = 9.5 days) and 1-15 (average duration = 11.5 days) days, respectively.

Changeover of therapy was done with an appropriate reason for 35 (10.8%) patients in internal medicine wards and 133 (46.66%) patients in surgery wards who had received IV PPIs for appropriate indications. Notably, changeover of IV PPI therapy to oral PPI or $H_2$-RA was done without stating any reason for 185 (57.1%) patients in internal medicine wards and 10 (3.51%) patients in surgery wards. In contrast, 104 (32.1%)

patients in internal medicine wards and 142 (49.83%) patients in surgery wards did not receive changeover of therapy, indicating over use of IV PPIs leading to treatment cost. Few (*n*=4, 1.23%, in internal medicine wards; *n*=12, 4.21%, in surgery wards) were on oral PPI therapy at the time of admission and were converted to IV PPI therapy without an appropriate reason (reason stated was stress ulcer prophylaxis).

Total cost per patient associated with prescriptions of IV PPIs in internal medicine wards was Rs. 60,229; average cost was Rs. 186. Total cost and average cost/patient associated with the prescriptions of IV PPIs in surgery wards was Rs.1,05,990 and Rs. 372, respectively.

## DISCUSSION

This study revealed significant inappropriateness of PPI administration with particular reference to indication to use, duration of therapy, and changeover of therapy in an Indian private tertiary-care teaching hospital. The most common cause for inappropriate use of IV PPIs was stress ulcer prophylaxis. Not surprisingly, the cost of treatment for patients who received IV PPIs with inappropriate indications or for prolonged duration without an appropriate indication was higher.

We noted a significant difference in the prescribing pattern of IV PPIs among different prescribers. Most inappropriate IV PPI prescriptions were ordered by postgraduate students (232(37.97%) patients), followed by junior doctors (112(18.33%) patients) and senior doctors (43(7.04%) patients). These results suggest the need for institutional protocols. This finding was in agreement[11] where in authors found that non-specialists, junior doctors and general practitioners had higher prescribing errors than specialists. In a retrospective cohort study of non-critically ill adults admitted to the internal medicine teaching service of a community hospital,[12] found that 58.5% patients received acid-suppressive medication to prevent stress ulcer bleeding though there was no evidence of GI bleeding.

The main strength of this study was that inappropriateness in prescribing patterns of IV PPIs was revealed by an unbiased prospective survey. To the best of our knowledge, this prospective survey is the first to reveal (a) significant inappropriateness with particular reference to indications to use IV PPIs and duration and changeover of IV PPI therapy, and (b) significant difference in the prescribing pattern among different prescribers in an Indian tertiary-care teaching hospital. In addition, this finding was in accordance with findings reported from other countries. For instance, 59-89 and 42-68 % of hospitalized patients received acid suppression therapy without appropriate indications in Sweden and Italy, respectively.[13,14] A 1-day survey at an Irish hospital revealed about 33% inappropriate indications.[15] In an American study, 71% of patients who received IV PPIs did not meet standard criteria for an appropriate indication for use.[2]

Despite this key finding, this study has a few limitations. First, this study took place in a single hospital over a one month period and there is no evidence that IV PPI over use is prevalent in other Indian hospitals. Therefore, variations in prescribing habits may exist as a result of the seasonal presentation of different patient populations and skills acquired by our physicians as the academic year cycles. Second, the study was purely observational and no attempt was made to intervene or educate formally our prescribers at any time. However, we felt that this initial prospective survey was required to establish the prescribing patterns to study further on the role of intervention on prescribing practice. Finally, we relied on the medical record documentation of doctors to discern their intentions and no attempt was made to question physicians on their reasons for prescribing IV PPIs. Although such data would have been of interest, but it was felt that a questionnaire would have biased sub sequent prescribing patterns during the prospective assessment, making the results uninformative. In the future, we hope to conduct a specific study to understand the role of (a) questioning and (b) intervention or medical education on the prescribing practice of prescribers in a tertiary-care teaching hospital.

These findings are a cautionary note regarding prescribing of IV PPIs and it would be sensible to recommend that their use be reserved only for patients having appropriate indications, as listed in Table 1. Developing IV PPI order templates that requires selection of an approved indication for use followed by pharmacist review and alert to the physician if there is an over use of IV PPI may improve the quality of prescribing practices. Appropriate prescribing practices of IV PPIs are likely to provide more cost-effective treatments.

## CONCLUSION

This prospective study revealed significant inappropriateness in prescribing patterns of IV PPIs in a tertiary-care hospital in India, leading to increased therapeutic burden and treatment cost. These data are valuable because they can be used to establish standard guidelines or order templates for the rational use of IV PPIs, and promote rational drug use in India and other developing countries.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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