Appropriateness of Intravenous Proton Pump Inhibitor Use in Labuan Hospital, Federal Territory of Labuan

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Abstract

Introduction: There are increasing concerns that intravenous (IV) proton pump inhibitors (PPIs) are being prescribed inappropriately in the hospital settings. Prolonged PPI therapy may cause hypergastrinemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy which may lead to rebound acid hypersecretion.

Objective: This study aimed to determine the appropriateness of IV PPIs use in two non-intensive care unit adult wards of Labuan Hospital.

Methods: All patients admitted to the two non-intensive care unit adult wards of Labuan Hospital who received IV PPIs during the seven-month study period were included in the study. Data collection was performed prospectively using a data collection form to collect data on patient demographics and information related to IV PPI prescription. The indication of IV PPIs recorded was compared against a set of "Appropriate indications for IV PPIs" developed based on the Ministry of Health Drug Formulary, product prescribing information, guidelines and published literature to assess the appropriateness of the indication.

Results: A total of 117 patients received IV PPIs during the study period. The most common indications for prescribing IV PPIs were gastritis (19.7%), prevention of drug-induced ulcer (19.7%) and gastrointestinal symptoms such as abdominal pain, nausea and vomiting (17.9%). Of the 117 patients, only 17 (15%) were prescribed with the appropriate indications. Among the 10 patients whom IV PPIs were indicated for upper gastrointestinal bleeding, all were identified to be appropriately indicated. However, when IV PPIs were prescribed for the prevention of drug-induced ulcer and gastrointestinal symptoms, the use of IV PPI was only considered appropriate in 4.4% and 4.8% of the patients respectively.

Conclusions: This study highlighted the inappropriateness of IV PPI utilisation in non-ICU patients in Labuan Hospital. Restriction of IV PPI use for justified indications and route of administration is recommended.

Keywords: quality use of medicine, Federal Territory of Labuan, proton pump inhibitor, appropriateness

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Introduction

Proton pump inhibitors (PPIs) are potent gastric acid suppressing agents (1). Currently, intravenous (IV) PPIs are approved for treating patients who are unable to tolerate oral medications due to gastroesophageal reflux disease (GERD) with a history of erosive esophagitis and in patients with pathological hypersecretory states with Zollinger-Ellison syndrome (ZES). They are also approved to reduce the risk of re-bleeding in gastric or duodenal ulcers following therapeutic endoscopy (2,3). In real life practices, the use of IV PPIs is not restricted to regulatory approved indications. They are been used in the treatment of high-risk peptic ulcers, complicated gastroesophageal reflux, stress-induced ulcer prophylaxis, and whenever it is impossible or impractical to give oral therapy (1,4).

There are increasing concerns that IV PPIs are being prescribed inappropriately in the hospital setting (1). Studies have shown that IV PPIs were prescribed inappropriately in 53 – 75% of cases (5-7). Such extensive use of unnecessary PPI therapy has led to the investigation of potential associated adverse effects. Retrospective studies found that the use of PPIs may be associated with adverse effects such as increased risk of enteric infections including *Clostridium difficile*-associated diarrhoea, community-acquired pneumonia, bone fracture, nutritional deficiencies, and interference with the metabolism of antiplatelet agents. Moreover, prolonged PPI therapy may cause hypergastrinaemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy which may lead to rebound acid hypersecretion (8).

With the increasing concerns regarding the adverse effects of PPI usage and the increasing pressure on the healthcare budget, it is important to investigate the indication for PPI treatment and to identify the factors of such extensive use (5,9). Previous review article documented that PPI overutilization in the inpatient setting was often a result of inappropriate stress ulcer prophylaxis (SUP) in non-intensive care unit (non-ICU) patients (10).

Currently, three IV PPIs are available in Labuan Hospital, which are Esomeprazole, Pantoprazole and Omeprazole. The average monthly usage of IV Esomeprazole and IV Pantoprazole were 49 vials and 136 vials respectively with an average cost of RM1,480 per month. IV omeprazole is reserved for paediatric patients and therefore not investigated in this study. As IV PPIs consume a considerable amount of the drug budget, it is important to ensure their appropriate usage. Hence, the objective of this study was to determine the appropriateness of IV PPIs use in two non-ICU adult wards of Labuan Hospital.

Methods

This is a prospective observational study which was conducted in two non-ICU adult wards of Labuan Hospital. The study was registered with the National Medical Research Register (NMRR) and the approval by the Ministry of Health Malaysia (MOH) Medical Research and Ethics Committee (MREC) was obtained prior to the initiation of the study.

The inclusion criteria of this study were patients more than18 years of age who were admitted in the two non-ICU adult wards (internal medicine, surgery, or orthopaedic) of Labuan Hospital, and received IV PPIs. Paediatric patients and outpatients were not enrolled in the study. Patients who were admitted to ICU before transferring to these two non-ICU wards were also excluded. Prescriptions of IV omeprazole were excluded as well as it was only reserved for paediatric patients.

One sample proportion level sample size formula has been used to calculate the sample size in this study (11,12): $n=Z^2P(1-P)/d^2$. We estimated a 95% confidence interval and a power of 80%. Therefore Z was 1.96 and d was 0.05. Based on the results of our 10 participant pilot study that was conducted in July 2016, it was estimated that 90% of the prescription of IV PPI was inappropriate. Therefore, we set the P as 0.9 and the calculated sample size was 138. We adjusted the sample size to account for dropouts (d set at 0.2) by using the formula: N1=n/(1-d). Based on above calculation, our targeted sample size was 180.

Table 1: Appropriate indications for IV PPIs

Appropriate indication	Dosage	Notes
1. Non-variceal upper gastrointestinal bleeding following therapeutic endoscopy	IV Pantoprazole / Esomeprazole 80mg STAT followed by an infusion of 8mg hourly for 72 hours	- It is appropriate in those who could not undergo an endoscopy for clinical reasons (clinically unstable or other comorbidity precluding endoscopy). - If re-bleeding occurred, diagnosed on clinical and / or endoscopic grounds, the patient is allowed to receive IV PPI for an additional 72 hours.
2. Gastroesophageal reflux disease in patient with esophagitis and/or severe symptom of reflux	IV Pantoprazole / Esomeprazole 40mg OD for up to 10 days	It is only appropriate when the oral route is not possible.
3. Healing of duodenal or gastric ulcer	IV Pantoprazole 40mg OD or IV Esomeprazole 20-40mg OD	It is only appropriate when the oral route is not possible.
4. Prevention of gastric and duodenal ulcers associated with nonsteroidal anti-inflammatory drug (NSAID) treatment, in patient at risk	IV Pantoprazole / Esomeprazole 20mg OD up to 10 days	It is only appropriate when the oral route is not possible.
5. Pathological hypersecretion conditions including Zollinger-Ellison syndrome	IV Pantoprazole 80mg BD-TDS or IV Esomeprazole 40mg BD	It is only appropriate when the oral route is not possible.

Abbreviation: STAT - immediately; OD – once a day; BD - twice a day; TDS - three times a day

The data collection was carried out over seven months (July 2016 – January 2017) using universal sampling method. Data such as gender, age, days of hospitalisation, past and current medical history, all concurrent medications during IV PPI administration, oral or nil by mouth (NPO) status during IV PPI use and information about IV PPI use (indication, duration, dose, specialty of the prescriber and prescriber status) were recorded using a structured data collection form. Both the medication charts and clinical notes were examined by the data collector to identify the indications of IV PPIs prescription.

The indication of IV PPIs recorded was then compared against a set of "Appropriate indications for IV PPIs" (Table 1). The appropriate indications were developed based on the Ministry of Health Drug Formulary, product prescribing information, relevant guidelines and published articles (5,13-19).

Results

A total of 181 patients were identified to have received IV PPI in the two non-ICU adult wards of Labuan Hospital from July 2016 to January 2017. Of those, 64 patients were discharged from the wards before the data collection by the investigators. Therefore, only 117 medication charts and clinical notes were reviewed.

Patient characteristics and the appropriateness of IV PPI indication were shown in Table 2 and Table 3. Male patient (73.5%) was more than female patient (26.5%). The mean patient age was 51 years old. Most of them were receiving IV Pantoprazole (97.4%). The number of patients from the medical discipline (80.3%) was more than the surgical (18.9%) and orthopaedic (0.9%). The reasons for hospital admission included gastric-related illness, infection, cardiovascular, hepatic, gastrointestinal, renal or pulmonary diseases. About one third (34.2%) of the patients received drugs which may induce gastric ulcer such as anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids during hospitalisation.

The most common indications for prescribing IV PPIs were gastritis (19.7%), prevention of drug-induced ulcer (19.7%) and gastrointestinal symptoms such as abdominal pain, nausea and vomiting (17.9%). Of the 117 patients that were prescribed with IV PPI, only 17 (15%) were prescribed with the appropriate indications while the indications for PPI in 100 (85%) patients were inappropriate. Among the 10 patients whom IV PPIs were indicated for upper gastrointestinal bleeding (UGIB), all were identified to be appropriately indicated. When the IV PPIs were indicated for GERD / peptic ulcer (5 patients), the indication was appropriate in 4 (80%) of the patients. Nevertheless, when IV PPIs were prescribed for the prevention of drug-induced ulcer and gastrointestinal symptoms, the use of IV PPI was only considered appropriate in 4.4% and 4.8% of the patients respectively.

Table 2: Characteristics of patients (N=117)

Characteristics	n (%) or mean (SD)
Gender, n (%)	
Male	86 (73.5)
Female	31 (26.5)
Age, year, mean (SD)	51 (17.5)
Length of stay, day, mean (SD)	7 (5.4)
Duration of IV PPI use, day, mean (SD)	4 (3.4)

Abbreviation: SD – standard deviation

Table 3: Appropriateness of IV PPI prescription (N=117)

Variable	Patient, n (%)	Appropriate IV PPI prescription, n (%)
Type of PPI prescribed		
Pantoprazole	114 (97.4)	14 (12.3)
Esomeprazole	3 (2.6)	3 (100.0)
Indication of IV PPI		
Gastritis	23 (19.7)	1 (4.4)
Prevent drug-induced ulcer	23 (19.7)	1 (4.4)
Unknown	23 (19.7)	0 (0.0)
GI symptoms	21 (17.9)	1 (4.8)
UGIB	10 (8.5)	10 (100.0)
Pancreatitis / cholecystitis	8 (6.8)	0 (0.0)
GERD / peptic ulcer	5 (4.3)	4 (80.0)
Anaemia	4 (3.4)	0 (0.0)
Diet status		
Oral	79 (67.5)	2 (2.5)
NPO	31 (26.5)	14 (45.2)
Tube feeding	7 (6.0)	1 (14.3)
Past medical history		
NKMI	42 (35.9)	3 (7.1)
Cardiovascular	38 (32.5)	7 (18.4)
Endocrine	12 (10.3)	2 (16.7)
Gastroenterology	8 (6.8)	1 (12.5)
Gastric related	7 (6.0)	4 (57.1)
Pulmonary	4 (3.4)	0 (0)
Renal	3 (2.6)	0 (0)
Others	3 (2.6)	0 (0)
Reason for hospital admission		
Infection	30 (25.6)	1 (3.3)
Cardiovascular	28 (23.9)	2 (7.1)
Gastroenterology	22 (18.8)	2 (9.1)
Gastric related	16 (13.7)	11 (68.8)
Pulmonary	6 (5.1)	0 (0.0)
Endocrine	4 (3.4)	0 (0.0)
Nephrology	4 (3.4)	0 (0.0)
Others	7 (6.0)	1 (14.3)
Concurrent medications		
One blood thinner	20 (17.1)	2 (10.0)
Two blood thinners	4 (3.4)	1 (25.0)
Three blood thinners	14 (12.0)	1 (7.1)
Corticosteroids	1 (0.9)	0 (0.0)
NSAIDs	1 (0.9)	0 (0.0)
No drugs that may induce gastric ulcer	77 (65.8)	13 (16.9)
Discipline		
Medical	94 (80.3)	13 (13.8)
Surgical	22 (18.9)	4 (18.2)
Orthopaedic	1 (0.9)	0 (0.0)
Prescriber status		
Medical officer	104 (88.9)	16 (15.4)
Specialist	13 (11.1)	1 (7.7)

Abbreviation: UGIB - upper gastrointestinal bleeding; GERD - gastroesophageal reflux disease; NPO - nil by mouth; NKMI - no known medical illness; NSAIDs - nonsteroidal anti-inflammatory drugs; GI – gastrointestinal

Discussion

This prospective study demonstrates that inappropriate utilisation of IV PPI therapy was quite frequent in the non-ICU wards at our institution when the indications for IV PPI were compared against a set of "Appropriate indications for IV PPIs". Only 15% of patients received appropriate IV PPI therapy. These results are in keeping with other studies found in the literature (5,7,20).

One of the reasons IV PPIs were prescribed inappropriately was the low adherence to the guidelines regarding PPI prescription (21). In a study carried out by White *et al*. in 2003, up to 36% of doctors were discovered to have prescribed IV PPIs without clear benefit, such as active lower gastrointestinal bleeding (LGIB) and variceal bleeding (22). Zink *et al.* 2005 found that 60% of patients were prescribed with acid suppression therapy without reason or with an inappropriate indication. Inappropriate indications given were low risk or gastrointestinal prophylaxis, pancreatitis, steroid use, LGIB, anaemia, vomiting, inflammatory bowel disease. In Labuan Hospital, most of the IV PPIs were prescribed without a documented indication (19.7%), for gastritis (19.7%), to prevent drug-induced ulcer without concomitant risk factor (19.7%) and to relieve gastrointestinal symptoms such as abdominal pain (17.9%) (23). Another reason for over-utilization of IV PPIs during hospitalisation was its safety and tolerable profile compare to the hazard of gastric ulcer. Ulcer complications can have serious consequences on health such as haemorrhage, confined and free perforation, gastric outlet obstruction and gastric cancer (23,24). The fear of development of ulcer encouraged the utilisation of IV PPIs. Concurrent intake of potentially gastro-toxic compounds might also a contributing factor (25).

It is important to note that IV PPIs is not recommended for stress ulcer prophylaxis (SUP) in non-ICU wards as patients in non-ICU wards rarely meet the two criteria for stress ulcer prophylaxis, namely coagulopathy and respiratory failure requiring mechanical ventilation for more than 48 hours (26-27). Indeed, the risk of bleeding in patients without these two criteria is as low as 0.1% and the prophylaxis can be safely withheld (27). While the guidelines for SUP in ICU patients have been well defined in the medical literature, the perceived benefit from SUP has been extrapolated to patients in non-ICU setting, leading to over utilisation of PPIs and increased overall healthcare costs. This happened when doctors feel that certain non-ICU patients are at a higher risk of developing stress ulcers, such as patients on chronic or high-dose steroids, patients who are septic or potentially septic, and it is easily preventable by PPIs without clear regard for cost-effective provisions of care. However, it is reasonable for clinical judgement to determine if a patient with moderate to severe physiologic stress in the non-ICU setting may ultimately benefit from PPIs, taking into consideration potential risks versus benefits, likelihood of stress ulcer development, cost-effectiveness, and certainly a plan for ensuring that patients are not discharged on PPI without appropriate symptoms or indications for treatment (10).

Grime *et al.* (2001) reported that PPIs were frequently prescribed for non-specific abdominal or chest pain and this was similar to our findings (28). Patients who were admitted for non-gastric related illness were significantly more prone to receiving unnecessary IV PPIs compared to patients who were admitted for gastric related issue. 28% of the patients who received IV PPIs were admitted for cardiovascular diseases such as angina, myocardial infarction, dyslipidaemia and hypertension. 32.5% of the patients were receiving one or more than one type of blood thinners, for example, aspirin. Doctors may prescribe PPIs when patients who receive prophylactic aspirin develop significant gastrointestinal disturbance due to aspirin or have history of peptic ulcer disease. However, this indication is not approved (29). Our study also found that inappropriate prescribing of IV PPI was more prevalent among patients with non-UGIB indications and this scenario also been reported in several other studies (5,7,20). It may be due to the fact that local clinical practice guideline for non-variceal UGIB has been published but not the other non-UGIB illnesses.

Throughout the study period, we found that most of the non-fasting patients were receiving other oral medications at the same time but were prescribed with IV PPI. In fact, both IV and oral PPIs have similar effects on inhibition of gastric acid secretion. Oral PPIs are as effective as IV PPIs except in bleeding peptic ulcer case which require a continuous infusion to achieve high target pHs to promote clot stabilization (1). In addition, oral PPI brings extra benefits compared to the IV formulation such as lower cost, reduced utilization of hospital resources, and fewer IV related complications (30). The additional costs of intravenous tubing, infusion pumps, and personnel time must be considered when giving IV PPIs to patients (31). These findings highlight the role of the clinical pharmacist in the selection of appropriate candidates for oral PPI.

Craig *et al.* reported that inappropriate prescribing was more common in female patients, surgical admissions and when initiated by junior hospital doctor (7). Nasser *at al.*, however, reported a contradicting result, in which they found that IV PPI was more likely to be inappropriately prescribed in medical rather than surgical department (30). Afif *et al.* found that there were relationships between increasing patient age, lower

mean daily PPI dose, timing of prescriptions and appropriateness of IV PPI therapy (5). However, these variables were not examined in this study.

There were several limitations in our study. Firstly, this study was observational and conducted at a single site, which may limit its generalizability. The results might be biased by the prescribing habits of a relatively small number of doctors. In addition, there were no current established guidelines for the appropriate use of IV PPI in the hospital to evaluate their actual use. Moreover, we assumed that patients with no clear documented indication for PPI use received the drug inappropriately. Since the data in our study were abstracted by chart review from each patient hospitalisation, it is possible that some appropriate utilisation of IV PPIs might be missed when the indications have not been documented in the patient chart.

Conclusion

This study found the high rate of inappropriate use of IV PPIs in Labuan Hospital. Inappropriate prescribing of IV PPIs was observed mainly when the indication was for the prevention of drug-induced ulcer and gastrointestinal symptoms. As a recommendation, we suggest that hospitals should consider developing controlled policies such as formulary restrictions, stop-orders for certain indications and automatic switch-order to oral PPI if patient is receiving oral feeding. At the same time, doctors and pharmacists may work together to review the need of IV PPIs during patients' hospital stay.

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Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

References

1. Pang SH, Graham DY. A Clinical Guide to Using Intravenous Proton-Pump Inhibitors in Reflux and Peptic Ulcers. *Therapeutic Advances in Gastroenterology* 2010; 3:11-22.
2. Prescribing Information for Nexium IV. AstraZeneca 2016.
3. Prescribing Information for Protonix IV. Pfizer 2014.
4. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock. *Society of Critical Care Medicine, European Society of Intensive Care Medicine*. 2013.
5. Afif W, Alsulaiman R, Martel M, Barkun AN. Predictors of Inappropriate Utilization of Intravenous Proton Pump Inhibitors. *Alimentary Pharmacology & Therapeutics.* 2007; pp 609–615.
6. Lai PMS, Wong YY, Low YC, Lau HL, Chin KF, Mahadeva S. Unexplained Abdominal Pain as a Driver for Inappropriate Therapeutics: an Audit on the Use of Intravenous Proton Pump Inhibitors. *PeerJ*. 2014; 451.
7. Craig DGN, Thimappa R, Anand V, Sebastian S. Inappropriate Utilization of Intravenous Proton Pump Inhibitors in Hospital Practice—a Prospective Study of the Extent of the Problem and Predictive Factors. *QJM*. 2010; 327-335.
8. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therapeutic advances in gastroenterology*. 2012; 219-232.
9. Moran N, Jones E, O'Toole A, Murray, F. The Appropriateness of a Proton Pump Inhibitor Prescription. *Irish Medical Journal*. 2013; 326-7.
10. Heidelbaugh J, Inadomi J. Magnitude and Economic Impact of Inappropriate Use of Stress Ulcer Prophylaxis in Non-ICU Hospitalized Patients. *American Journal of Gastroenterology*. 2006; 2200-2205.
11. Al-Subaihi AA. Sample size determination: Influencing factors and calculation strategies for survey research. *Neurosciences*. 2003; 8(2):79-86.
12. Suresh K, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. *Journal of human reproductive sciences*. 2012; 5:7-13.
13. Kaplan GG, Bates D, McDonald D et al. Inappropriate Use of Intravenous Pantoprazole: Extent of the Problem and Successful Solutions. *Clinical Gastroenterology and Hepatology.* 2005; 1207-1214.
14. Cheer SM, Prakash A, Faulds D, Lamb HM. Pantoprazole. *Drugs*. 2003; 101-132.
15. Prescribing Information for Nexium IV. AstraZeneca 2016.
16. Prescribing Information with Medication Guide for Nexium. AstraZeneca 2008.

17. Prescribing Information for Pantosec IV. Cipla 2013.
18. Clinical Practice Guidelines: Management of Non-Variceal Upper Gastrointestinal Bleeding. 2003.
19. Pharmaceutical Services Programme, Ministry of Health Malaysia. Ministry of Health Malaysia Drug Formulary. 2017. Available at: https://www.pharmacy.gov.my/v2/en/apps/fukkm
20. Sebastian S, O'Morain CA, Qasim A. Appropriateness of Gastric Antisecretory Therapy in Hospital Practice. *Irish journal of medical science*. 2003; 115-117.
21. Magadmi EM, Alnabulsi RK, Dhabab NM, Alsubahi TA, Basheikh MA, Kamel FO. Practice toward and knowledge about proton pump inhibitor prescription in Jeddah, Saudi Arabia. *International Annals of Medicine*. 2018; 2(6).
22. White KT, Storch IM, Mullin GE. Intravenous Pantoprazole: Physician Understanding of Indications and their Prescribing Patterns Leading to Hospital Restrictions. *The American Journal of Gastroenterology*. 2003; S231.
23. Zink DA, Pohlman M, Barnes M, Cannon ME. Long-term Use of Acid Suppression Started Inappropriately During Hospitalization. *Aliment PharmacolTher*. 2005; 1203-1209
24. Vakil N. Peptic ulcer disease. *Merck Manual Professional Version*. 2016.
25. Parente F, Cucino C, Gallus S, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. *Aliment PharmacolTher*. 2003; 1503-1506.
26. Alsultan MS, Mayet AY, Malhani AA, Alshaikh MK. Pattern of intravenous proton pump inhibitors use in ICU and non-ICU setting: a prospective observational study. *Saudi Journal of Gastroenterology*. 2010; 16(4): 275–279.
27. Cook DJ, Fuller HD, Guyatt GH et al. Risk Factors for Gastrointestinal Bleeding in Rritically Ill Patients. *N Engl J Med*. 1994; 377-381.
28. Grime J, Pollock K, Blenkinsopp A. Proton Pump Inhibitors Perspective of Patients and their GPs. *British Journal of General Practice*. 2001; 703-711.
29. Choudhry MN, Soran H, Ziglam HM. Overuse and Inappropriate Prescribing of Proton Pump Inhibitors in Patients with *Clostridium Difficle*-Associated Disease. QJM. 2008; 445-48.
30. Nasser SC, Nassif JG, Dimassi HI. Clinical and Cost Impact of Intravenous Proton Pump Inhibitor Use in Non-ICU Patients. *World Journal of Gastroenterology*. 2010; 982-6.
31. Barletta JF, Erstad BL, Fortune JB. Stress Ulcer Prophylaxis in Trauma Patients. *Critical Care*. 2002; 526-530.