SJP Sarawak Journal of Pharmacy

Journal Homepage: http://jknsarawak.moh.gov.my/spj/

PRESCRIBING PATTERN OF ORAL PROTON PUMP INHIBITORS IN SIBU REGION, A MULTICENTRE STUDY

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ABSTRACT

Introduction: Strong evidences supporting the proton pump inhibitors (PPIs) efficacy has led to an overprescribing of PPIs globally. Recently, the reported adverse events of PPIs had arrested safety issues. This study carried out to determine the prescribing pattern of oral PPIs in Sibu government primary care settings.

Methods: In this cross-sectional study, all PPIs prescriptions received at outpatient pharmacy from 1st October to 31st October 2017 and fulfilled the inclusion criteria reviewed with patient's clinic card to determine the appropriateness of PPIs prescribing. Patients' demographics, type of PPIs, indication, dosage, duration, prescribing discipline, concurrent medications and cost recorded.

Results: According to our study, we found that 52.96% of the oral PPIs inappropriately prescribed for its indication. In our setting, PPIs mostly prescribed as gastrointestinal prophylaxis in patients on NSAIDs, including low dose aspirin (47,17%). Therefore, we

assumed that patients receiving low-dose aspirin and NSAIDs may be a trigger for inappropriate PPI prescriptions in our setting. Our study also showed that 62.34% of the PPIs were prescribed for >52 weeks. It arrested our attention that benefits over the risks of long-term PPI use should be assessed. We found that PPIs mostly prescribed inappropriately in patients <65 years old and those on ≥5 concurrent oral medications (p<0.001). Besides, orthopaedic department contributed the most inappropriate prescription of oral PPIs (p<0.001). From our study, we estimated that inappropriate prescribing of oral PPIs has led to expenditure of RM 24,864.83 per year.

Conclusion: Remedial actions such as assessing the indication to initiate oral PPIs and the need for ongoing PPIs use could be implemented to curb the inappropriate PPIs use.

Keywords: *prescribing, proton pump inhibitors, appropriateness*

INTRODUCTION

Proton pump inhibitors (PPIs) are the most effective medications currently available to reduce gastric acid secretion. PPIs have emerged as the leading treatment for gastro-oesophageal reflux disease (GERD), upper gastrointestinal bleeding secondary to peptic ulcer disease or non-steroidal anti-inflammatory drug (NSAID)-induced ulcer, *Helicobacter* pylori eradication, dyspepsia and hypersecretory disorders such as Zollinger-Ellison syndrome. Besides, they are widely used for stress ulcer prophylaxis, as well as the prophylaxis of gastrointestinal (GI) bleeding in patients on NSAIDs or dual antiplatelet therapy.

The strong evidence supporting the PPI efficacy and a well-tolerated safety profile has led to an overprescribing of PPIs globally (1-7). Their use is widespread and on the increasing trend, with annual sales worldwide that have exceeded US $25 billion (1). In Germany, the PPIs' prescribing raised from 44 million defined daily doses (DDD) in 1993 to 1,674 million DDD in 2008, accounted for a drastic increase of 3,805%, cost 540 million Euros per year (1). According to Malaysian Statistics on Medicine 2009-2019, drugs for acid-related disorders ranked as 8th in the expenditures on therapeutic drug groups. In 2010, by ranking of expenditures on drugs in Malaysia, omeprazole ranked number 10 (cost RM57.2 million per year), pantoprazole ranked 14th (cost RM53.9 million per year) and esomeprazole ranked 27th (cost RM35.3 million per year). All these frequently used PPIs had fall into the top 50 drugs by expenditures in 2010 (8).

According to few Western studies carried put recently, the prevalence of PPI overprescribing has been reported to be between 61 to 86% in the hospital setting (6, 7). Additionally, a recent study from a tertiary hospital setting in Singapore reported that only 45.9% fulfilled the indications of PPI as approved by FDA (5). A multicenter prospective study carried out in France in 2014 showed that the overprescribing of PPIs found in 73.9% older patients (10).It is also common for the duration of use of PPIs to be longer than necessary once started (9). A recent study from a tertiary hospital in Malaysia found that

52.8% of the IV PPIs were inappropriately prescribed in patients for its indication, dose or duration (13).

The increased in PPI prescribing patterns could be influenced by doctors' consideration that patients are at a higher risk of developing stress ulcer especially those who are on NSAIDs, aspirin, corticosteroids, those receiving chemotherapy and elderly people (10, 11). A cross-sectional observational study conducted in 35 primary care practices in North-Eastern Germany found that 54.5% of PPIs were prescribed without valid indications upon discharge (1). Patients are then often discharged from hospital on oral PPIs as a result of inappropriate stress ulcer prophylaxis (SUP) in non-intensive care unit, and failure to discontinue SUP prior to hospital discharge, leading to a significant increase in expenditures and patient exposure to risk of adverse effects (14).

Recently, a search of the WHO International ADR database revealed that the reported adverse events of PPIs involve the safety issues under the review of National Pharmaceutical Regulatory Agency, such as subcutaneous lupus erythematosus, hypomagnesaemia, osteoporotic fractures, and risk of pneumonia, *Clostridium difficile* infection, and dementia (12). A meta-analysis of nine studies involving 115,455 patients found statistical significance between PPI use and the risk of hypomagnesaemia (17). In a meta-analysis of 11 international observational studies, PPIs modestly increased the risk of hip, spine, and any-site fractures (18). Besides, in one meta-analysis of 23 studies encompassing 300,000 patients, PPI use increased the incidence of *Clostridium difficile* infection by 65% (15). A systematic review of 33 studies and meta-analysis of 26 studies spanning over 20 years reported that outpatient use of PPIs was found to confer a 1.5-fold increased risk of developing community-acquired pneumonia (16). A large scale longitudinal observational study published recently examining the link between PPI use and the risk of developing dementia in the German population has revealed a significantly increased risk of dementia with regular use of PPIs (19).

Hence, the study of the prescribing pattern of PPIs in the local setting was imperative as a consequence of the rising issues of the potential adverse effects with long-term use of PPIs. Many studies had been done to date regarding the pattern of PPI prescribing practice in Malaysia. However, the current literature illustrated a spectrum of variations in the prescribing pattern, reflecting a respective local prescribing pattern and patient demographic in different communities. Methodological approaches chosen by different investigators also largely inconsistent. Hence, these statistics could not be extrapolated to Sibu government primary care settings.

This study carried out to determine the prescribing pattern of oral PPIs in Sibu Hospital and also three main government health clinics in Sibu area. This study might provide clinically meaningful statistics of local prescribing pattern that serves as a helpful feedback for prescribers in hospital and health clinics. This study might also serve as a preliminary study, providing a first-step and basis in the area for future pharmacist-led intervention in improving the prescribing pattern of PPIs.

METHODS

Study Type and Design

In this cross-sectional study, all new prescriptions received at the outpatient pharmacy during the period between 1st October and 31st October 2017 was screened for PPIs. Prescriptions for paediatrics (below 12 years old) and walk- in patients as well as those with incomplete case record and clinic card or home based card was not available were excluded. Those containing PPIs included in this study and reviewed by pharmacists. Indications of oral PPI considered appropriate for use or accepted for use were pre-defined in definition as shown in Table 1 and 2 respectively. Other indications than those mentioned in Table 1 and 2 considered as inappropriate or no clear indications.

Data collected at the time patient collect medications in outpatient pharmacy so patient's clinic card or home based card was available for investigator to collect relevant data. Both the prescriptions and patient's medical record in clinic card or home based card were examined to determine the rationale for prescription. History of peptic ulcer or gastrointestinal bleeding and *Helicobacter pylori* infection were determined based on endoscopy result and diagnosis in patient's medical record. Patients' demographic data (age, gender), type of PPIs, indication, prescribed dose, frequency and the date the PPI started as well as the prescribing discipline, concurrent medications and cost were recorded using a structured data collection form.

Sample Size

According to World Health Organization recommendation on sample size, there should be at least 600 encounters included in a cross-sectional study for a drug utilization survey. Therefore, the minimum sample size required in this study is 600 patients.

Statistical Analysis Plan

Statistical analysis performed using the Statistical Package for the Social Science (SPSS version 20.0). Descriptive analysis used to describe prevalence of inappropriate oral PPI prescribing. Continuous data expressed as mean ± SD. Categorical variables were expressed as absolute (number) and relative frequencies (percentage). Categorical data analysed using chi-squared tests. A p-value of <0.05 considered as statistically significant.

Ethics of Study

This was a case record review study of past prescription. Patient was not interviewed. Risk and benefit to study participants were not an issue. Approval received from Medical Review and Ethics Committee (MREC) of the Ministry of Health Malaysia before commencement of this study.

RESULTS AND DISCUSSSION

Prevalence of inappropriate indications of oral PPIs prescribed (Table 3).

Based on our study, it showed that about half of the PPIs (52.96%) were prescribed for inappropriate indications such as prescribed with unknown reason or for other indications like gastric cancer, epigastric pain, pancreatitis and acute gastroenteritis. A similar study carried out in Singapore also showed that about half of the PPIs prescribed did not have clear indication (5). PPIs overutilization remains prevalent in many countries. According to a data pooling from 34 international studies published between 2000 and 2016 with PPIs being prescribed, the extent of inappropriate use of PPIs range from 11% to 84% with average of almost half of PPI prescriptions might be inappropriate (24).

PPIs were most likely prescribed for NSAIDS prophylaxis (47.17%) in our study. Current guidelines recommend peptic ulcer prophylaxis in patients on NSAIDs with ≥ 1 risk factor(s) which are (20):

1. Previous history of a gastric ulcer
2. Age >65 years
3. Previous history of *H. pylori* infection
4. Concurrent use of aspirin (including low dose)
5. Concurrent use of corticosteroids
6. Concurrent use of anticoagulants
7. Concurrent use of antiplatelets

According to our study, we found that nearly half of the patients on NSAIDs/aspirin prescribed with PPIs were without GI risk factor.

Duration of PPIs prescribed (Table 4)

From our study, it described more than half (62.34%) of PPIs were prescribed for duration more than 52 weeks, with NSAIDs prophylaxis topped the list. Long term use of PPIs has recently become an issue for it increasing risk of various adverse effects including risk of *Clostridium difficile* infection, hip fracture and dementia (12, 18, 19, and 25). Hence, the risk and benefit of PPIs use in long term should be assessed.

Doctors may not be aware of existing guidelines and thus, use PPIs in without clear indications. Inappropriate assumptions about the risk of ulcer development during hospitalization may also be an explanation for the overprescribing of PPIs for long term (1). Prolonged use of PPIs has always been related to stress ulcer prophylaxis (SUP) during hospitalization, then the PPIs inappropriately continue upon discharge (14). The resulting PPIs were prescribed for longer duration without justifiable indication as prescribers might not be aware of the ongoing prescribing of PPIs during patient follow up in clinic as outpatients.

Predictive factors leading to inappropriate prescribing of oral PPI (Table 5)

Association of PPIs use with age

Our study found that PPIs mostly prescribed for patients aged 41-65 (49.2%) followed by patients aged over 65 (44.4%). It showed that patients aged 41-65 was associated with high prescription of PPI. Our study found that PPIs were mostly prescribed inappropriately in patients 13-40 (78.3%). The inappropriate indication of PPI among patients aged >65% was least likely. There were clinical and epidemiological data showed that the incidence of NSAID and aspirin related ulcers increases with age (26). This data consistent with the explanations of other studies that increased PPI prescribing could be influenced by doctors' consideration that elderly is at a higher risk of developing stress ulcer especially those who are on NSAIDS, aspirin or corticosteroids (10, 11).

Hence, use of PPIs in elderly justified. However, the appropriateness to prescribe PPIs in young populations should be assessed.

PPIs used according to disciplines

In our study, PPIs were most commonly prescribed by the medical discipline (73.1%), followed by the orthopaedic (11.8%) and surgical (8.4%) discipline. Among these departments, orthopaedic department contributed the most inappropriate prescription of oral PPIs ($p<0.001$), followed by medical. Given the magnitude of the problem of inappropriate PPI usage in orthopaedic and medical practice, remedial measures to improve the situation should be considered. For orthopaedic department, we might suggest the PPI usage on "when necessary" (prn) basis only if it is indicated for GI prophylaxis against NSAIDs which intended to be taken when necessary too. Prescriber should assess the risk and benefit of PPIs use especially in those patients without taking any concurrent medications with GI risk or in young populations.

Another possible approach would be to educate the departments most associated with the inappropriate PPI use in hospitals. Pharmacists in the wards could monitor the PPI usage during hospitalization and upon discharge. This could help to limit the PPI use for patients with more appropriate indications as the pharmacists could suggest discontinuing the PPIs when it is no longer indicated.

Association of PPIs used with number of concurrent medications

Our study also showed that more than half (67.9%) of the PPIs were prescribed with concurrent oral medications ≥5. PPIs were mostly prescribed inappropriately in those on ≥5 concurrent oral medications ($p<0.001$). Hence, number of concurrent medications was significantly associated with PPI prescribing. This conclusion was in agreement with the result of another study, which found that number of concurrent medications was higher in patients who were overprescribed a PPI than in patients with

an appropriately prescribed PPI (*p*=0.018) (27). These results could be explained by patients receiving multiple medicines were likely under follow up of several specialists (27); however, no scientific evidence exists suggesting the need for PPI therapy in patients receiving multiple medicines.

Prevalence of PPI prescribed in patient on concurrent medications with GI risk (Table 6)

Our study showed that 79.7% of patients on steroids prescribed with PPIs inappropriately. There is a theoretical benefit of reducing gastric pH with PPIs to prevent steroid-induced peptic ulcers. Thus, the use of steroid is commonly associated with the use of PPI to prevent gastrointestinal bleeding; however, no scientific evidence exists suggesting the need for this therapy in the absence of other risks factors. Meta-analyses found that peptic ulcer is, at the most, a rare complication of systemic corticosteroid therapy occurring in less than 0.4-1.8% of patients. As the incidence is low, routine prophylaxis with PPI is not indicated for systemic corticosteroid therapy unless patient has concomitant medications of NSAIDs, or patient is on high dose steroid (2,10, 30-33).

Then, there were 61.1% of patients on warfarin were prescribed with PPIs inappropriately. According to literature, for warfarin patients, only those with previous gastrointestinal bleeding, those having *H pylori* infection, taking concomitant medications associated with GI ulcers (eg. NSAIDs, corticosteroids) or those with high risk of bleeding (based on bleeding score such as HAS-BLED bleeding score) warrant the consideration of PPI co-prescription (34).

Besides, 52.1% of patients on NSAIDs were prescribed with PPIs inappropriately. Gastroprotective medication is recommended to be given to patient on NSAIDs if they have comorbid diseases such as cardiovascular diseases, aged more than 65 years old, has past history of peptic ulcer disease, prolonged use of maximal dose of NSAIDs and those who take concomitant oral steroids (29).

Therefore, we could assume that low-dose aspirin or NSAIDs in low-risk patients including those <65 years, patients receiving steroid therapy, oral anticoagulant and/or antiplatelet treatment may have been a frequent trigger for inappropriate PPI prescriptions in our setting.

Cost Effectiveness of PPIs (Table 7)

According to our study, inappropriate use of PPIs consumed a total amount of RM24,864.83 per year. It has arrested our attention as PPIs are a major burden for the national healthcare budget according to Malaysian Statistics on Medicine. A study has showed that different PPIs are considered to be equally effective in inhibiting gastric acid secretion at equipotent dose (27). Therefore, we recommend using pantoprazole in our setting which is cheaper but equally effective compared to other PPIs.

LIMITATIONS

Even though we had full access to patient's home-based card, electronic medical records (PHIS) including all previous prescriptions, procedures, and investigations, we acknowledged that this might have resulted in an overestimation of inappropriate PPI use if we determined the appropriateness of an indication based on physician documentation and merely exploring clinical records alone. Besides, we might also underestimated the number of PPI prescriptions with actual indications by assuming the indications as unknown or likely GI prophylaxis as it was possible that some of these prescriptions might have been justified by physicians during patient interviewing or assessment, but were not documented in medical records.

CONCLUSION

In conclusion, this study serves as a preliminary study reviewing the prescribing pattern of oral PPIs in Sibu region. Although our study could not conclusively justify the appropriateness of PPIs prescribed to our outpatients solely based on prescription and clinic card review, worldwide widespread and inappropriate use of PPIs caught our attention to take some remedial actions. Undoubtedly, healthcare costs and the accompanying financial burden as well as the side effect of PPIs would escalate due to the inappropriate initiation and maintenance of patients on PPIs. Remedial actions such as assessing the indication to initiate the oral PPIs and reviewing the need for ongoing PPI use by prescribers could be implemented to curb the inappropriate PPI use.

CONFLICT OF INTEREST

The investigators declared they have no conflict of interest.

Table 1. Indications of oral PPI considered appropriate for use (evidence-based):

INDICATION	CRITERIA FOR INDICATION
Treatment of upper GI bleeding (UGIB) or peptic ulcer	Patients with major peptic ulcer bleeding (active bleeding or non-bleeding visible vessel) following endoscopic haemostatic therapy (21, 22)
Treatment of gastroesophageal reflux disease (GERD) or dyspepsia	A chronic condition in which the lower esophageal sphincter allows gastric acids to reflux into the esophagus, causing heartburn, acid indigestion, and possible injury to the esophageal lining (22, 23)
For *H. pylori* eradication	Test for the presence of *H. pylori* and eradicate if present (22)
	Ref : NHS guidelines

Table 2. Other accepted indications for the use of oral PPI

INDICATION	CRITERIA FOR INDICATION
Prophylaxis of NSAIDs (including low dose aspirin) related GI ulcer	Patients on NSAIDs with ≥ 1 risk factor(s): 1. Previous history of a gastric ulcer 2. Age >65 years 3. Previous history of H. pylori infection 4. Concurrent use of aspirin (including low dose) 5. Concurrent use of corticosteroids 6. Concurrent use of anticoagulants (20)
Uninvestigated dyspepsia/ gastritis (empirical treatment)	Treatment of symptomatic gastritis without evidence from endoscopic investigations (5, 20)

Table 3. Indication appropriateness of oral PPIs prescribed (n =725)

Indication	Appropriate indication n (%)	Accepted indication n (%)	Inappropriate/ no clear indication n (%)	Total n (%)
GI ulcer				**25 (3.45)**
Esomeprazole	1 (0.14)	0	0	1 (0.14)
Omeprazole	5 (0.69)	0	0	5 (0.69)
Pantoprazole	19 (2.62)	0	0	19 (2.62)
GERD				**13 (1.79)**
Esomeprazole	1 (0.14)	0	0	1 (0.14)
Omeprazole	3 (0.41)	0	0	3 (0.41)
Pantoprazole	9 (1.24)	0	0	9 (1.24)
Dyspepsia				**18 (2.48)**
Esomeprazole	2 (0.28)	0	0	2 (0.28)
Omeprazole	5 (0.69)	0	0	5 (0.69)
Pantoprazole	11 (0.15)	0	0	11 (0.15)
H. pylori eradication				**4 (0.55)**
Esomeprazole	1 (0.14)	0	0	1 (0.14)
Omeprazole	0	0	0	0
Pantoprazole	3 (0.41)	0	0	3 (0.41)
NSAIDS				**342 (47.17)**

prophylaxis				
Esomeprazole	0	5 (0.69)	5 (0.69)	10 (1.38)
Omeprazole	0	33 (4.55)	24 (3.31)	57 (7.86)
Pantoprazole	0	157 (21.66)	118 (16.28)	275 (37.93)
Gastritis				**86 (11.86)**
Esomeprazole	0	3 (0.41)	0	3 (0.41)
Omeprazole	0	20 (2.76)	0	20 (2.76)
Pantoprazole	0	63 (8.69)	0	63 (8.69)
Others				**97 (13.38)**
Esomeprazole	0	0	1 (0.14)	1 (0.14)
Omeprazole	0	0	9 (1.24)	9 (1.24)
Pantoprazole	0	0	87 (12.00)	87 (12.00)
Unknown				**140 (19.31)**
Esomeprazole	0	0	1 (0.14)	1 (0.14)
Omeprazole	0	0	28 (3.86)	28 (3.86)
Pantoprazole	0	0	111 (15.31)	111 (15.31)
Total	**60 (8.28)**	**281 (38.76)**	**384 (52.96)**	

Table 4. Duration of oral PPIs prescribed (n =725)

Indication	<2 weeks n (%)	2-4 weeks n (%)	5-8 weeks n (%)	8-52 weeks n (%)	>52 weeks n (%)
GI ulcer	0	1 (0.14)	2 (0.28)	6 (0.83)	16 (2.21)
GERD	1 (0.14)	2 (0.28)	0	2 (0.28)	8 (1.10)
Dyspepsia	0	0	0	4 (0.55)	14 (1.93)
H. pylori eradication	0	0	1 (0.14)	1 (0.14)	2 (0.28)
NSAIDS prophylaxis	3 (0.41)	10 (1.38)	10 (1.38)	111 (15.17)	208 (28.69)
Gastritis	1 (0.14)	8 (1.10)	2 (0.28)	17 (2.34)	58 (8.00)
Others	2 (0.28)	3 (0.41)	5 (0.69)	28 (3.72)	59 (8.14)
Unknown	0	5 (0.69)	5 (0.69)	43 (5.93)	87 (12.00)
Total	7 (0.97)	29 (4.00)	25 (3.45)	212 (29.24)	452 (62.34)

Table 5. Predictive factors leading to inappropriate prescribing of oral PPI such as characteristics of patient, patient's concurrent medications and prescribers' discipline.

Predictive factors		***n***	**Appropriate indication of PPI n (%)**	**Inappropriate indication of PPI n (%)**	**χ^2 statistic[a]**	***P* value[a]**
Gender	Male	337	170 (50.4)	167 (49.6)	0.552 (1)	0.458
	Female	388	185 (47.7)	203 (52.3)		
Age (years)	13-40	46	10 (21.7)	36 (78.3)	135.042 (2)	0.000
	41-65	357	110 (30.8)	247 (69.2)		
	>65	322	235 (73.0)	87 (27.0)		
Prescriber's discipline	Medical	530	236 (44.5)	294 (55.5)	56.360 (4)	0.000
	Surgical	61	50 (82.0)	11 (18.0)		
	Orthopaedic	86	31 (36.0)	55 (64.0)		
	FMS	42	35 (83.3)	7 (16.7)		
	Others	6	3 (50.0)	3 (50.0)		
Number of concurrent oral medications	≤1	42	34 (81.0)	8 (19.0)	20.406 (2)	0.000
	2-4	191	100 (52.4)	91 (47.6)		
	≥5	492	221 (44.9)	271 (55.1)		

[a] Chi-square test for independence

Table 6. Prevalence of inappropriate indication of PPI prescribed in patient on concurrent medications with GI risk

Concurrent medications	Appropriate indication (%)	Accepted Indication (%)	Inappropriate indication (%)
NSAIDS	1.7	46.2	52.1
Aspirin	4.3	60.4	35.3
Ticlopidine	0	54.5	45.4
Clopidogrel	4.3	60.9	34.8
Warfarin	1.9	37.0	61.1
Steroid	1.7	18.6	79.7

Table 7. Cost expenditure associated with the appropriateness use of oral PPIs.

	Esomeprazole	Omeprazole	Pantoprazole	Total
Expenditure with appropriate use, RM (%)	1918.48 (31.7)	2296.35 (38.0)	1830.08 (30.3)	6044.91 (100)
Expenditure with accepted use, RM (%)	3387.92 (14.6)	9995.40 (43.1)	9791.66 (42.3)	23174.98 (100)
Expenditure with inappropriate use, RM (%)	1490.08 (6.0)	10231.51 (41.1)	13143.24 (52.9)	24864.83 (100)

ACKNOWLEDGEMENT

Sincere gratitude to Chang Poh Yin, Monica Ho Ai Fong, Yew Kiu Ping, Lim Chuen Lu, Cooghen Dev, Chan Pui Sheon, Winnie Too, Jenny Ting Siau Li, Adeline Lau Chiaw Chiaw for collecting the data required for this study.

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