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Original Article

Gastrointestinal Side Effects of Proton Pump Inhibitors on Inpatients at Gatot Soebroto Hospital

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ABSTRACT

Introduction: Gastrointestinal side effects of proton pump inhibitors (PPI) medicines can be diarrhea and constipation. **Objective:** The purpose of this study was to prospectively analyse gastrointestinal side effects of PPIs used by inpatients of Gatot Subroto Hospital. **Material and Methods:** This descriptive analytic study collected data prospectively from prescriptions and patient medical records and through an interview with valid and reliable questionnaire. Causality analysis of gastrointestinal side effects was done by using Naranjo Algorithm while Chi-square and Fisher absolute test were used to see the association between gastrointestinal side effect and gender, age, PPI's dose, and duration of administration of PPI. Samples were patients who were ≥ 17 years old, received proton pump inhibitor and signed the Informed Consent. **Results:** The data were collected from February to April 2016 by total sampling method. From 58 patients as research samples, nineteen patients (32.75%) experienced constipation which 16 patients (27.58) and 3 patients (5.17%) were with probable and possible category, respectively. None experienced diarrhea. There were no significant association between constipation and sex, age, PPI's dose and the duration of PPI's. **Conclusion:** Constipation was the most common gastrointestinal side effect that was not related to age, sex, PPI dose, and duration of PPI administration.

Key words: Constipation, Naranjo algorithm, Proton Pump Inhibitor, Side effect, Dengue high fever, Gatot Soebroto hospital.

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INTRODUCTION

Proton pump inhibitors (PPIs) are the most powerful agent of suppressing gastric acid secretion and function by inhibiting H+,K+-ATPase (proton pump) of the stomach. These medications reduce the production of stomach acid from 80% to 90%. PPIs are intended for the treatment of gastric and duodenal ulcers and to treat gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome (ZES), and as a component in a related treatment of *Helicobacter pylori* (*H. pylori*) infection[1]

PPIs became known in 1989 for the treatment of peptic ulcer disease. Omeprazole is a common drug which until recently, was one of the most widely prescribed drugs worldwide. Following the release of omeprazole in the market, other types of PPIs were launched-lansoprazole (1995), pantoprazole (1997), rabeprazole (1999), and esomeprazole (2001).[2] A study showed that PPI drugs are some of the most widely prescribed drugs worldwide in both primary treatment and secondary treatment; yet, approximately 25–70% of patients taking this drug do so without proper indication.[3]

The guidelines of the National Institute of Clinical Excellence (NICE) on PPI therapy recommend regular monitoring of patients receiving PPI therapy to assess their need for the drug and maintenance therapy with lower doses or other alternative medicines to control symptoms.[4] The percentage of gastrointestinal side effects of PPI such as diarrhoea and constipation are 3–4% and 1–2%, respectively.[5] Reduction of acid production due to the use of PPIs can cause microorganisms to colonize in the upper gastrointestinal tract. Enteric infection is often associated with *Clostridium difficile (C.difficile)*, which causes gastroenteritis and even death.[6] PPI use with *C. difficile* is associated with diarrhoea. Diarrhoea is the most common side effect reported from the long-term use of PPI medications. The range of diarrhoea incidence reported is from 3.7% to 4.1%.[7] Another study states that the rate of side effects of constipation due to the use of PPIs is at 10%.[8] Gastrointestinal diseases can have an effect on the quality of life of patients as well as their healthcare utilization. Results of another study stated that the percentage of gastrointestinal complaints amounted to 61.7%, 14.9% of which were due to constipation.[9] Therefore, it is important to monitor drug side effects. The purpose of this study was to prospectively analyse gastrointestinal side effects of PPIs used by inpatients of Gatot Subroto Hospital.

METHODS

Study Design

This is a descriptive analytic study; data were collected prospectively from prescriptions and patient medical records, and primary data obtained through interviews using a valid and reliable questionnaire. The population in this study comprises the data of all inpatient of the Department of Internal Medicine at Gatot Soebroto Hospital from February to April 2016. The sample was the data of all inpatients in the Department of Internal Medicine at Gatot Soebroto Hospital from February to April 2016 who met the inclusion criteria. Inclusion criteria in this study are the data of patient's ≥17 years old who received PPI and were willing to participate in the study by signing the informed consent. Exclusion criteria are the data of patients who left before treatment was completed, patients who experienced diarrhoea or constipation prior to being hospitalized, and prescriptions or medical records that were unclear or could not be read. Patients with dropout criteria are patients who could not be monitored and those who died during treatment. The history of PPI use was obtained from medical records or patient interviews.

METHODS

Data were analysed using the Naranjo algorithm[10] to analyse causality in unwanted drug reactions. Univariate analysis was performed to obtain frequency of characteristics of the patients according to demographic and clinical factors, such as gender, age, primary diagnosis, and history of PPI use. Bivariate analysis was done to determine the association between age, sex, PPI dose, and duration of PPI administration with gastrointestinal side effects by using the chi-square test.

RESULTS

The total number of patients who received PPIs when hospitalized in the Department of Internal Medicine at Gatot Soebroto Hospital from February to April 2016 are 91 patients. A total of 25 patients were included in the exclusion criteria, of which 19 had diarrhoea and 6 experienced constipation before entering the hospital. Four patients were not willing to be the subject of research. A total of 62 patients were part of the inclusion criteria. Four patients were excluded as subjects of research (drop out) due to death during hospitalization; thus, the total number subjects of research were 58 patients.

Patient Characteristics

The age range of patients in this study is 20–81 years old. Majority of the research subjects were female (58.6%), and many of them within an age range of 46–55 years old (41.4%). The most primary diagnosis from the subject of this study are patients with DHF (Dengue High Fever) as many as 15 patients (25.9%). Seven patients (12.1%) with dyspepsia, and one patient (1.7%) with stroke. In all, 15 patients (25.9%) had received PPIs prior to being hospitalized, 11 patients (18.9%) never received PPIs prior to being hospitalized, and 32 patients (55.2%) had an unknown history of PPI use (Table 1.)

In this study, all of the subjects were given omeprazole with the total 110 therapies. Omeprazole with a dose regimen of 2 x 20 mg and 1 x 40 mg are the most widely used with the percentage 39.10% and 37.27% respectively. Omeprazole therapy with 2 x 20 mg dose regimen that use fewer than two weeks is the most widely used (37, 28%), while 1 x 40 mg dose regimen is 34.55%. Total of oral route administration were 52 therapies (47.28%), and intravenous routes were 58 therapies (52.72%).

Gastrointestinal Side Effect

From the secondary data, such as prescriptions and medical records, as well as primary data from patient interviews, 19 patients experienced constipation. The side effect of diarrhoea was not found in the subjects. On the basis of analysis from the Naranjo algorithm, it was found that 16 patients (27.58%) were in the probable category and 3 patients (5.17%) were in the possible category for experiencing gastrointestinal side effects such as constipation.

The chi-square test with significance value (two-sided) showed no association between gender, age, PPI dose, and duration of PPI administration with gastrointestinal side effects.

Table 1: Charcateristics of patients

	Category	Total of Patient (N=58)	Percentage (%)
	Gender		
1.	Male	24	41,4
2.	Female	34	58,6
	Age		
1.	17 – 25 years old	9	15,5
2.	26 – 45 years old	17	29,3
3.	46 – 65 years old	24	41,4
4.	>65 years old	8	13,8
	History of PPI's use		
1.	Had received PPI	15	25,9
2.	Never received PPI	11	18,9
3.	Unknown	32	55,2
	Primary Diagnosis		
1.	DHF	15	25,9
2.	Dyspepsia	7	12,1
3.	Diabetes Mellitus	7	12,1
4.	CKD	4	6,9
5.	Anemia	4	6,9
6.	Sepsis	3	5,2
7.	Ascites	3	5,2
8.	Chronic Gastritis	2	3,4
9.	Appendics	2	3,4
10.	Cirrhosis Hepatic	2	3,4
11.	Typhoid fever	1	1,7
12.	Brain Tumor	1	1,7
13.	Stomach Tumor	1	1,7
14.	AIDS	1	1,7
15.	Thrombocitopenic	1	1,7
16.	Stroke	1	1,7
17.	Hematemesis Melena	1	1,7
18.	GERD	1	1,7
19.	Angioedema	1	1,7

*AIDS (Acquired Immune Deficiency Syndrome)
DHF (Dengue Heart Fever)
GERD (Gastroesophageal Reflux Disease)
CKD (Chronic Kidney Disease)

DISCUSSION

This result was contrary to study at a Hospital in India in 2015 [11], majority of this research subjects were female (58.6%), and many of them within an age range of 46–55 years old (41.4%). Where as at Hospital in India, most of PPI were prescribed for male (56%) with a mean age group of 50-60 years (26%).[11]

The percentage of patients who suffer from constipation in this study was quite high compare to other studies[9,12,13] After 8 weeks of PPI treatment, 2% of patients complained of diarrhoea, while after 6 months of treatment, 17% patients experienced diarrhoea and 2% reported constipation.[9] The percentage of gastrointestinal side effects due to PPI therapy according to the American Pharmacist Association was 2% with constipation and 3–4% with diarrhea.[5] A study from McCrea *et al.* (2009) showed that the prevalence of constipation in women is higher than in men.[13]

The percentage of the elderly age group category in this study who experienced side effects was higher (37.5%) than the adult age group (32%). In this study, there were no reported gastrointestinal side effects such as diarrhoea; this may be due to the duration of PPI use having been less than 2 weeks. Another study showed that 19 of the 489 patients who received PPIs for more than 30 days or >4 weeks complained of side effects such as *C. difficile*–associated diarrhoea.[13]

CONCLUSION

Constipation was the most common gastrointestinal side effect that was not related to age, sex, PPI dose, and duration of PPI administration.

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CONFLICT OF INTEREST

No conflict of interest are declare.

ABBREVIATIONS USED

PPI: Proton Pump Inhibitor; **GERD:** Gastro Esophageal Reflux Disease; **ZES:** Zollinger Ellison Syndrome; **H pylori:** Helicobacter pylori; **NICE:** national Institute of Clinical Excellence; **C.difficile:** Clostridium difficile; **DHF:** Dengue high Fever; **AIDS:** Acquired Immune Deficiency Syndrome; **CKD:** chronic kidney disease.

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