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Original Research Article

Utilization Review of Anti-peptic Ulcer Drugs at an Outpatient Pharmacy Setting of a Private Hospital in Malaysia

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ABSTRACT

Anti-peptic ulcer drugs (APUDs) such as proton pump inhibitors (PPI), H2 receptor antagonists (H2A), antacids are widely prescribed. This study is aimed to describe the utilisation pattern of APUDs based on WHO Defined Daily Dose (DDD) and identify most commonly used APUD in the selected hospital. A retrospective study was carried out in outpatient of the selected hospital for year 2017. Sample size was calculated using Raosoft. DDD of APUDs and direct drug cost were calculated. Data were collected through electronic medical record by retrieving patients' registration number. Inclusion criteria were patients above 18 years old and APUDs prescribed for gastrointestinal related indications. A total of 160 prescriptions were randomly selected for data analysis. Based on the DDD calculated, Rabeprazole 20mg was most prescribed drug among PPI (n=33), while Maalox is most prescribed drug among the antacids (n=23). Based on the DDD calculated, Pantoprazole 20mg recorded highest rates per user per day about 1.26 DDD / user / day while antacids, Actal reported highest usage rate with 7.11 DDD / user / day. Besides, there are 5.4 days supplied per user for this drug. Dexlansoprazole 60mg is the most expensive drug among all the PPI listed in hospital formulary. It has 18.5 days supplied/user, which is the second shortest duration of treatment among all the other PPIs. In contrast, omeprazole 20mg is the lowest cost PPI but the duration supplied per user is longer resulting in higher total cost of therapy. In conclusion, PPIs were the most commonly prescribed.

INTRODUCTION

Peptic ulcer disease (PUD) has been common ailment, where annual incident report stated 0.03% to 0.17% were diagnosed by medical examiner and treated as outpatient and 0.03% to 0.17% during hospital stay. The incidence of PUD has decline on recent time in some countries, this is attributed to the decrease in Helicobacter pylori infection, particularly in Western populations [1]. Asian countries recorded lower peptic acid disorder prevalence rate compared to advance nation meanwhile Malaysian recorded prevalence 9.5% for duodenal ulcer and 9.4% gastric ulcer respectively [2].

Reports on prevalence and incidence of peptic ulcer secondary to geographical variation exists with differences in relative occurrences of duodenal and gastric ulcers. Ethnic variations on peptic ulcer incidence has been reported on the pattern of peptic ulcer in Malaysia from endoscopic data at University Medical unit at Kuala Lumpur that states Chinese of both gender have a higher susceptibility to peptic ulcer [3].

Anti-Peptic Ulcer Drugs (APUDs) such as H2-receptor antagonists (H2RA), proton pump inhibitors (PPI), and antacids are commonly used by medical partitioner, on other hand synthetic prostaglandins and cytoprotective agents has been promptly used by gastroenterologist in private clinics. Besides peptic ulcer disorder this agents are also used in

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treatment non-ulcer dyspepsia and heartburns. These group drugs are co-prescribed as prophylaxis agents during nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, anti-platelet and anticoagulation therapy [4]. Many physicians had raised concern regarding adverse events due to long-term acid suppression therapy. n other hand with PUD drug endoscopic study reveal 30% of patient suffered with peptic ulcer whom co-prescribed NSAIDs [5]. Therefore, there is a need to develop a policy on APUD and drug formulary.

Common acid suppressants used in gastrointestinal disorders are PPI and H2RA. The trend of drug consumption in Malaysia has transformed significantly from H2RA to PPI and currently, there are overconsumption of PPI [6]. A huge number of patients, as many as 90% in one study consume these drugs with no appropriate guideline-based indication [7]. Since PPIs are easily available, this makes them one of the most widely prescribed medications; thus irrational use and unnecessary exposure prone to happen. Long-term consumption of a proton pump inhibitor may lead to gastric carcinoids and increases the risk of hip fractures [8]. Moreover, PPIs are costly thereby increasing the economic burden on the patients. PPI over usage has become very critical, where this study need to be commenced in order to provide a better understanding in healthcare sector [9].

According to Kandasami, the total cost of PUD patient prescription surges as more than half of patients suffering from peptic ulcers are usually associated with comorbidities that necessitates treatment [10]. Although the prevalence of acid related disorders in Malaysia is in the region of 8-10%, , only 0.6% of the population have been prescribed with medications for acid related diseases by Malaysian Society of Gastroenterology and Hepatology. This shows that there is a treatment gap. Therefore, there is a need to standardise treatment algorithms for acid related disorders in Malaysia and the important role of anti-peptic ulcer drugs in the management of acid related disorders needs to be clearly defined.

The over-prescribing of APUD highlighted the importance of the need to examine the current utilization and appropriateness of the anti-peptic ulcer drugs. The outcome of this study will be beneficial to develop a policy on APUD usage and drug formulary at the selected hospital. Drug utilization review may help the prescribers to interpret, understand, and expand the prescribing, administration and usage of the medication. This may directly have a positive impact on patient health and financial status.

METHOD

Overview of Research Design

A retrospective observational study on drug utilization of anti-peptic ulcer drugs had been carried out in the outpatient department of a private hospital located at Seremban, Negeri Sembilan Malaysia. A retrospective study design that trace information backwards was used. The selected hospital uses KPJ Clinical Information System (KCIS) and Hospital Information Technology System (HITS) which is the Electronic Medical Record (EMR).

KCIS creates a boundless communication among the healthcare professionals which manages the clinical aspects of the hospital, while HITS is a system of the hospital management that integrates all patients' information since the patient been registered until billing from KPJ Annual Report. These systems are used to obtain data that are needed for this study. Inclusion and exclusion criteria were applied to select the appropriate drug utilisation data.

Patient selection criteria

Prescriptions from newly registered patients as well as regular follow-up patients were included in the study according to the inclusion and exclusion criteria. Prescriptions that fulfilled the following inclusion and exclusion criteria adopted from literature were included [11].

Inclusion criteria

- Prescription with patient more than age of 18 years old receiving anti-peptic ulcer drugs.
- Pharmacologically treated for peptic ulcer with or without comorbidities.

Exclusion criteria

- The prescription with incomplete patient data for data collection form.
- Non-KPJ prescriptions.

Sampling Method

The sampling technique that has been used in this study were block randomization as well as convenience sampling. Block randomization method was used to randomize subjects into groups that result in equal sample sizes. Then, in order to choose the sample, convenience sampling was used.

Sample study

The sample size required for this study was estimated based on a formula stated by Daniel [12]. For this study, the significance level was set at α = 0.05 (two tailed) and 95% degree of confidence interval (CI) fixed in the calculation sample size by using the formula as stated above. The minimum sample size calculated was 138 patients with peptic ulcer from the outpatient department.

Variable Definition

The KPJ Clinical Information System (KCIS) was used to access the list of all patients that are previously prescribed with anti-peptic ulcer drugs in 2017 and record in a data collection form. Only prescriptions that met the inclusion and exclusion criteria were included in this study. So, these patients' prescriptions records were retrieved between January till December 2017 by using their medical record number (MRN) or identification card number (IC).

The following data were collected for each prescription: Demographic data which includes the age, sex and weight of patient, diagnosis and relevant prescription data. This includes the name of medication, pharmacological class, dose prescribed, dosage regimen which includes frequency and route of administration and number of drugs per prescription. The collected prescriptions were evaluated based on criteria of prescription and standard guideline on DDD.

The prescription was assessed based on the following criteria, number of drugs prescribed, number prescribed in generics, dose strength, dosage of drug and duration of therapy. Meanwhile, the guideline on DDD that was used as the main reference in this study are CPG of Non-variceal Upper Gastrointestinal Bleeding and National Drug Formulary.

Defined Daily Dose Formula

The Defined Daily Dose (DDD) for a drug is its assumed average maintenance dose per day for a drug used as a main indication in adults as WHO guideline (Eq. 1).

$$Total\ DDDs = \frac{Dosage\ form\ strength\ \times\ Quantity\ of\ drug\ dispensed}{WHO\ assigned\ DDD\ for\ the\ drug} \quad (Eq.1)$$

To provides a rough estimate of the proportion of the population treated daily with a specific drug, rates per residents per day is calculated using Eq.2.

$$DDDs\ per\ day\ per\ 1000\ residents = \frac{DDDDs\ per\ year}{30\ days\ \times\ 30{,}000\ residents} \times 1000 \quad (Eq.2)$$

To determine whether the DDD is close to the average daily maintenance dose for the drug's main indication (as determined by WHO), the rates per user per day is calculated (Eq.3)

$$DDDs\ per\ day\ per\ user = \frac{DDDDs\ per\ year}{30\ days\ \times\ Number\ of\ users} \quad (Eq.3)$$

Use of DDDs Clinically

A clinical measure can also be calculated to help interpret the DDDs/user/day value which assumes dispensation to users over an entire year. This can be done in two steps:

Firstly, an intermediate rate of the number of days supplied per user is calculated by summing the number of days supplied recorded on each prescription claim and dividing by the number of users.

Secondly, the measure of how the drug is actually being used was calculated by dividing the rate of the DDDs per user by the rate of the number of days supplied per user which is also known as DDDs / day supplied.

Outcome Parameter

The DDD between the standardized DDD by WHO were compared with DDD based on the drugs prescribed by the prescribers and patient's characteristics. The DDD/1,000 inhabitants/day which expressed as DDD methodology and the drug classification system, Anatomical Therapeutic Chemical (ATC) were used in estimating the usage of APUD in the selected private hospital. Data of DDD of APUD in the selected hospital were then analysed and compared to the standard DDD of WHO classification of ATC/DDD.

Ethical Consent

The ethical approval for this study was obtained from the Research Ethic Committee of KPJ University College, Nilai, Malaysia (KPJUC/RMC/BPH/EC/2017/100). This approval has been obtained before conducting the study. All data obtained were used solely for research and be kept confidential.

RESULT

Patients' selection and description

The prescription data that have met all the inclusion criteria were critically analysed. From the total outpatient prescriptions in 2017, 200 prescriptions were found matched the criteria based on the studies requirement and 22 prescriptions were excluded due to the diagnosis as Helicobacter pylori positive. However, due to some incomplete data were found, only 160 prescriptions were finally chosen.

Demographic Characteristics of Patients

Table I shows the demographic characteristics of the populations in this study and depicts that the most common age group in which APUDs were prescribed in both male and female was 50-59 years 31.88% (n=51) whereas the least age group prescribed with APUDs are below 20 years, 3.13% (n=5). The prescriptions of these drugs were slightly more among male patients 55% (N = 88) compared to female patients 45% (n=72). The major ethnicity found to be prescribed the most were Malay 63.75% (n=102) followed by Chinese 18.75% (n=30) and Indian 17.50% (n=28).

Table I. Gender and ethnicity of population based on age category

Category	Number of APUDs prescriptions, n (%)	
	Male n=88	Female n=72
Age category		
Below 20	2 (1.25)	3 (1.9)
20 to 29	2 (1.25)	4 (2.5)
30 to 39	12 (7.5)	12 (7.5)
40 to 49	27 (16.9)	16 (10)
50 to 59	30 (18.8)	21 (13.1)
Above 60	15 (9.4)	16 (10)
Ethnicity		
Malay	59 (36.9)	43 (26.9)
Chinese	16 (10)	14 (8.8)
Indian	13 (8.1)	15 (9.4)

Patterns of Anti-Peptic Ulcer Drugs Utilization

In this study, the number of drugs prescribed varied according to the severity of patient condition and requirement of therapy. Drugs prescribed per prescription among 160 patients ranged from 1 to 2 types of drug products.

Table II illustrates the utilization pattern of anti-peptic ulcer drugs according to their classification and it reveals that most common class of anti-peptic ulcer drug prescribed to adult population in that corresponding hospital setting was proton pump inhibitors which accounted for 82% (n=159) followed by Antacids about 18% (n=35) and no usage of H2 antagonist.

Table II. Frequency of anti-peptic ulcer drug prescribed by medical officer and consultant.

Drug Classification	Drugs	Consultant	Medical officer
Proton pump inhibitor (82%, N=159)	Dexlansoprazole 60 mg	28	0
	Esomeprazole 40mg	27	2
	Omeprazole 20mg	21	6
	Pantoprazole 20mg	18	11
	Pantoprazole 40mg	9	4
	Rabeprazole 20mg	31	2
Antacid (18%, N=35)	Actal Tablet	5	0
	Maalox Suspension	17	6
	Zellox Suspension	6	1

The drug utilization was further examined specifically based on each type of drug products. PPI was the one most commonly prescribed drug class, 17% (n=33) was contributed by rabeprazole 20mg whereas the least usage of drug under the PPI category is pantoprazole 40mg, about 6.7% (n=13). Besides, the main PPI prescribed by consultant is rabeprazole 20mg while the most frequent PPI prescribed by medical officers is pantoprazole 20mg. The distribution of anti-peptic ulcer drugs utilization varied based on the strength of medication. The highest maximum usage of antacids is Zellox suspension, about 11.9% (n=23) whereas the least prescribed is Actal tablet about 2.6% (n=5).

Figure I demonstrates 40% (n=64) of prescriptions administered combination of anti-peptic ulcer drugs whereas 60% (n=96) of them administered a single APUD. The highest number of samples administering single group of APUDs are from the age group of 50 to 59 years old.

Frequency of anti-peptic ulcer drugs prescriptions from various department are illustrated in Figure II. It shows that out of the 160 prescriptions of APUDs, most number of outpatient prescriptions were found in general surgery department 26.9% (n=43) followed by 23.1% (n=37) from general medicine department. On the other hand, APUDs were least prescribed in urology, otorhinolaryngology (ENT) and obstetrics and

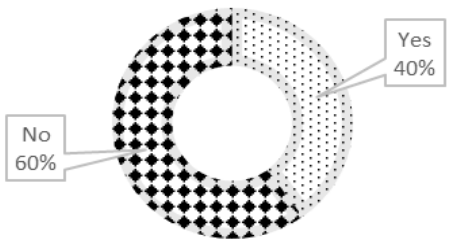

Figure I. Percentage of sample administering combination of anti-peptic ulcer drugs

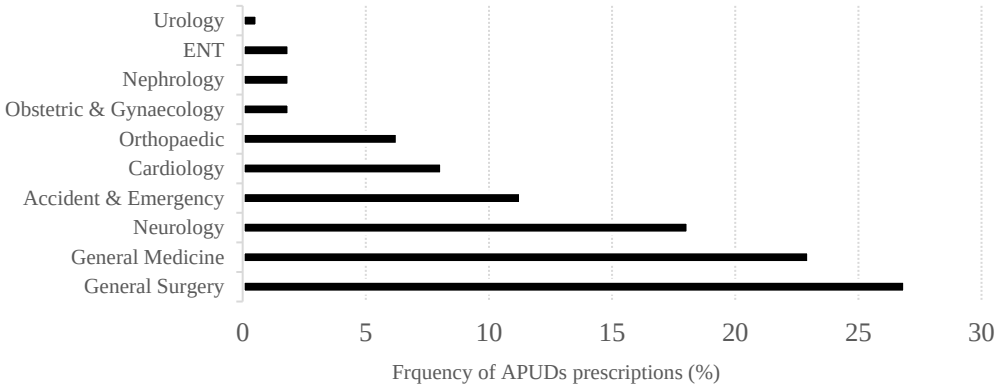

Figure II. Distribution of anti-peptic ulcer drug prescriptions of the study in outpatient department

gynaecology.There are two different categories of physicians commonly prescribe APUDs in the particular hospital which local and internationally educated physicians. Education background of a physician, indirectly related to the type of APUDs prescribed by the physician. Consultants from local and oversea education background for specialist training prefer different types APUDs for their patients. The most of APUDs prescribed by consultants form local universities are esomeprazole 40mg, 10.3% (n=20) whereas consultants from oversea universities prefer rabeprazole 20mg, 11.9% (n=23). In this hospital, all of the medical officers are from local universities and the highest number of APUDs prescribed by medical officers from local universities are pantoprazole 20mg, 5.7% (n=11).

Demographic variables and types of anti-peptic ulcer drugs prescribed

The frequency of anti-peptic ulcer drugs prescribed varies according to the age categories of patients. Table III show the diverse number of APUDs prescribed to the different age categories of patients. The most commonly APUD prescribed for patients below 20 years is Pantoprazole 20mg, 1.5% (n=3) and two types of APUDs are among 20 to 29 years old patients, pantoprazole 20mg and Omeprazole 20mg, 1.03% (n=2). Next, Omeprazole 20mg is the maximum usage of drug among 30 to 39 years old, 3.09% (n=6) whereas among 40 to 49 years old patients is esomeprazole 40mg, 6.2% (n=12). The highest amount of APUD accounted among 50 to 59 years old patients is rabeprazole 20mg, 6.7% (n=13) however among the age group of more than 60 years are two different APUDs, omeprazole 20mg and dexlansoprazole 60mg about 3.6% (n=7). Furthermore, the highest APUDs users belongs to age group of 50 to 59 years old.

Defined Daily Dose (DDD) of Anti-Peptic Ulcer Drugs (APUDs)

Table IV shows the results obtained from the calculation of DDDs / days supplied per user of APUDs at the selected hospital. Based on the DDD calculated, pantoprazole 20mg was the most prescribed drug among proton pump inhibitors (PPI) whereas Actal tablets has the highest usage among the antacids. There are differences in all the anti-peptic ulcer drugs usage although the difference among APUDs are significantly low. Although ranitidine from H2 antagonist is available in the drug formulary of the hospital, it is never been prescribed during the study period. Besides, there is a clear comparison among unit price of APUDs and it shows that dexlansoprazole 60mg is the highest cost PPI whereas Maalox 250ml is the highest cost antacid available.

DISCUSSION

Demographic Characteristics of Patients

In this retrospective study, a total of 160 prescriptions were reviewed as per the inclusion and exclusion criteria. In term of gender of the patients receiving the prescriptions, there are higher population of male patients, around 55 % and 45% are female patients. According to Department of Statistics Malaysia, there are 1.12 million of total populations in Negeri Sembilan and there are slightly more males (555,935) residents in the state capital city of Seremban. Cigarette smoking may lead to decrease in the circulating growth factor as well as rise of free radical production in gastric mucosa and it becomes the prominent factor of peptic ulcer disease [13]. Although smoking data was not available in this study, however the higher number of male patients is possibly related to increased smoking habit.

Among Malay, Chinese and Indian ethnics, there are greater number of Malay patients in this study and it is due to a vast difference in the distribution of ethnic groups in Negeri Sembilan: Malay (61.35%), Chinese (23.2%) and Indian (15.45%). Ethnicity predisposition differences does not alter the gastric acid secretion among peptic acid patients. The frequency of anti-peptic ulcer drugs usage increases with age as depicted in Table 1 whereby the highest number of APUDs prescribed in both male and female was in the 50-59 years age group. Study has confirmed that age group is not a risk factor of peptic ulcer disease, however, stress due to numerous health complications in this age group is described as the main source of peptic ulcers, which are termed as stress induced ulcers [13]. Evidence has suggested that Helicobacter pylori infection plays a major contributory role in peptic ulcer disease and preliminary studies have reported that the incidence of Helicobacter pylori infection increases with age [14].

Anti-Peptic Ulcer Drugs Utilization Patterns

According to Narayanan, management of peptic ulcer disease (PUD) has improved tremendously following the administration of proton pump inhibitors and therapy for Helicobacter pylori eradication [15]. This revealed from the decline in the incidence of Helicobacter pylori-associated PUD, and the lower percentage of Helicobacter pylori infection, particularly in complicated PUD. Table 2 shows the variety and proportion of anti-peptic ulcer drugs found in the study prescriptions. Most common class of anti-peptic ulcer drug prescribed was PPIs followed by antacids with no usage of H2 antagonist. Of all these drugs, rabeprazole 20mg was prescribed the most whereas the least prescribed was pantoprazole 40mg. The maximum usage of antacids in the hospital is Zellox suspension 100mL whereas the least usage is Actal tablet. Ranitidine was the only H2 blocker that was found in the hospital but there is no any usage of ranitidine during the study period. A recent meta-analysis displayed the effectives of PPI therapy by a drop of re-bleeding rate and frequency of surgery in patients with upper gastrointestinal bleeding following successful endoscopic therapy, compared to H2RA therapy. [16] Additionally, PPIs were superior to H2RAs for prevention of LDA-associated GI erosion or ulcer as according to another meta-analysis [16].

Figure I demonstrates higher population are administering single group of APUD, primarily PPIs whereas only 40% of them are prescribed combination of APUDs. Irrational use of PPIs alone should be avoided because few studies proved that the usage of PPIs alone can cause detrimental to the consumers. In two randomized controlled trials (RCTs), it is evident on the presence of dyspepsia in 20% to 44% of healthy volunteers after discontinuation of four to eight weeks of PPI therapy. Furthermore, as according to a systemic review, long-term practice of PPIs for more than two years is linked with an increased risk of vitamin B12 deficiency due to the alteration of intragastric pH levels. Observational data based systemic reviews and meta-analyses shown a connection between chronic PPI usage with the risk of fractures in both male and

Table III. Distribution of anti-peptic ulcer drugs prescriptions according to patients' age

Anti-peptic ulcer drugs	Patient's Age Group (n)					
	<20	20-29	30-39	40-49	50-59	60>
Actal Tablet	1		1	1	2	
Dexlansoprazole 60 mg		1	2		10	7
Esomeprazole 40mg			5	12	8	4
Maalox Suspension			1	1	4	1
Omeprazole 20mg		2	6	4	8	7
Pantoprazole 20mg	3	2	5	8	8	3
Pantoprazole 40mg	1	1	2	1	4	4
Rabeprazole 20mg		1	4	9	13	6
Zellox Suspension 100ml	2	1	4	5	8	3

Table IV. DDD/day supplied and unit price of each anti-peptic ulcer drugs

Type of APUDs	WHO DDD	Rates per residents per year	Rates per user per day	Intermediate rate	Clinical measure	Unit price (RM)
Pantoprazole 20mg	2 DDD	0.12	1.26	17.76	0.07	4.60
Pantoprazole 40mg	1 DDD	0.04	0.82	22.38	0.04	6.00
Dexlansoprazole 60mg	0.5 DDD	0.03	0.32	18.50	0.02	8.50
Esomeprazole 40mg	0.75 DDD	0.08	0.86	30.10	0.03	2.80
Omeprazole 20mg	1 DDD	0.09	0.95	28.37	0.03	1.00
Rabeprazole 20mg	1 DDD	0.11	1.01	30.33	0.03	5.10
Actal tablets	11.11 DDD	0.12	7.11	5.40	1.32	1.30
Zellox 100ml	0.38 DDD	0.03	0.37	11.05	0.03	30.00
Maalox 250ml	0.13 DDD	0.04	0.15	8.86	0.02	37.50
Pantoprazole 20mg	2 DDD	0.12	1.26	17.76	0.07	4.60

female patients. Whereas, this connection has not seen with the use of H2 receptor antagonists [17]. Alternatively, a H2 antagonist or over-the-counter antacids should be tried before prescribing the most potent PPIs because according to table 3, highest number of population administering single group of APUDs are from the age group of 50 to 59 years old and according to a nationwide case-control study from New Zealand, estimated there were about 20 cases of acute interstitial nephritis per year among every 100 000 current PPI users with more than 60 years old [18]. Thus, as an early preventive measure, it is better to prescribe H2 antagonist for patients with the age group of more than 50 years old.

Figure II shows that out of the 160 prescriptions of APUDs, most prescriptions were from general surgery department followed by general medicine department. On the other hand, APUDs were least prescribed in nephrology and otorhinolaryngology (ENT). This observation was justified in accordance to a study done at North India where the surgeon may prescribe acid reducers such as H2 Antagonists and PPIs to ease any discomforts after surgery. Likewise, it has been proven that a standardised prescribing of APUDs after surgery lead to significant reduction in postoperative complications such as postoperative pain, nausea and vomiting [19]. Similarly, high utilization of these APUDs was also seen in general medicine department because the use of PPI according to FDA is indicated as in cases of evident GI diseases comprise of treatment of symptomatic gastroesophageal reflux disease (GERD), maintenance treatment of erosive esophagitis, eradication of Helicobacter pylori infection, healing and maintenance of gastric ulcers, prevention and treatment of NSAID-induced gastric ulcers and treatment of hypersecretory condition as Zollinger-Ellison syndrome [20].

This study also indicated that rabeprazole 20mg is the most prescribed PPI in the hospital and followed by esomeprazole 40mg because rabeprazole and esomeprazole increase cure rates compared to pantoprazole, omeprazole and lansoprazole, the first generation PPIs. This advantage of new-generation PPIs has been reported earlier in reviews and retrospective studies and these new PPIs has been reported to affect eradication rates due to the higher acid inhibition power. Meanwhile, the clinical advantage may be restricted from a cost-effective perspective due to higher prices of rabeprazole and esomeprazole when compared with omeprazole [21]. In contrast, pantoprazole 40mg has the minimum usage amongst all the PPI. The results of a comparative study on esomeprazole 40mg versus pantoprazole 40mg illustrates a therapeutic advantage of esomeprazole 40 mg over pantoprazole 40 mg by providing healing of erosive esophagitis (EE). This result predicted as the healing of EE is inversely related to gastric acidity, and esomeprazole has been shown to deliver a greater suppression of gastric acidity than standard doses of all other PPIs [22].

McNicholl, states that five studies compared the eradication rates of rabeprazole versus esomeprazole [21]. The comparison was not heterogeneous and found no statistically significant differences. Rabeprazole has the eradication rates about 76.7% while esomeprazole shows 78.7%. According to a meta-analysis, CYP2C19 phenotype is not affected by the eradication rates of esomeprazole and rabeprazole, while first-generation PPIs demonstrates a clearer tendency towards lower eradication rates in patients. Meanwhile, majority APUDs prescribed by medical officers from local universities are Pantoprazole 20mg because it was approved by FDA in 2000 for the treatment of erosive esophagitis associated with GERD and PUD plus it is one of the few PPIs existing in multiple dosage forms. According to Mathews, pantoprazole has an excellent safety profile, is as effective as other PPIs, and has a low incidence of drug interactions when evaluated over 100 clinical trials. Pantoprazole has also been presented as a safe and effective among special patient populations, such as the elderly and those with renal or moderate liver disease [23].

Defined Daily Dose (DDD) and unit price of APUDs

In order to avoid recurrences of both symptoms and mucosal lesions, PPI is one of the mandatory maintenance therapy. Table IV clearly demonstrates DDD / day supplied for all the APUDs used and the result justified that APUDs over usage did not occur in this hospital. This demonstrates that several patients discontinue PPI therapy after redeeming their first prescription, whereas only a minority administer PPI continuously. Based on the DDD calculated, Pantoprazole 20mg reported highest rates per user per day among proton pump inhibitors (PPI) about 1.26 DDD / user / day. The maximum usage of this drug can be due to the compulsory triple regimen inclusive of pantoprazole for Helicobacter pylori eradication. Furthermore, administration of the slow-release pantoprazole results in the significantly faster onset of action taking place compared to the administration in a form without retarding such release [24]. In addition, Actal reported highest rates per user per day among the antacids, which is about 7.11 DDD / user / day. This can be seen clearly due to the lowest cost among all the antacids available in this hospital. Besides, there are 5.4 days supplied per user for this drug which shows much less duration than the other two different antacids. Thus, it is known as cost effective drug which indirectly reduce burden for the patients.

According to Table IV, dexlansoprazole 60mg is the most expensive drug among all the PPI listed in hospital formulary and it has 18.5 days supplied / user, which is the second shortest duration of treatment among all the other PPIs. This is because, dexlansoprazole is a modified-release drug because the active ingredients are manufactured in the form of two types of granules, which are released from capsule twice, at dissimilar pH values. One part of the drug dose, is released in the proximal

duodenum at more acidic pH, significantly at pH level of 5.5 while the second part of drug dose are released in the distal small intestine at the lesser acidic pH, significantly at the pH of 6.75. This twofold release mechanism enable the drug to attain two peak serum concentrations of the drug. Therefore, this modified release drug ensures the longer drug retention period in the circulation as well as the most dominant inhibitory effect on the proton pump inhibitors. Besides, numerous clinical trials states that dexlansoprazole has a good safety profile and hardly produces adverse reactions which usually do not require drug discontinuation because safety profile of dexlansoprazole at doses of 30, 60 and 90 mg plus oral administration has been assessed in clinical trials covering a period of 1 year [25]. In contrast, omeprazole 20mg is the lowest cost PPI but the duration supplied per user is longer resulting in higher total cost of therapy. Thus, dexlansoprazole could potentially the most cost-effective PPI although the single capsule is most expensive among all the other PPIs.

CONCLUSION

In conclusion, the obtained result of utilization of all anti-peptic ulcer drugs in the selected hospital is lower as compared to WHO DDD. However, this might not show an underutilization of anti-peptic ulcer drugs but may be due to a lower number of samples collected, which cannot be used to reflect the overall utilization. Next, most common class of anti-peptic ulcer drug prescribed in this studies were Proton Pump Inhibitors which accounted for 97% followed by Antacids about 32.5% and no usage of H2 Antagonist. Based on the DDD calculated, Pantoprazole 20mg was the most prescribed drug among PPI, about 1.26 DDD / user / day. Actal is the most commonly used drug among the antacids, which is about 7.11 DDD / user / day. The distribution of anti-peptic ulcer drug prescriptions in outpatient department was highest used in general surgery 26.9% and general medicine 23.1% department. Dexlansoprazole 60mg is the most expensive drug among all the PPI listed in hospital formulary. It has 18.5 days supplied/user, which is the second shortest duration of treatment among all the other PPIs. In contrast, omeprazole 20mg is the lowest cost PPI but the duration supplied per user is longer resulting in higher total cost of therapy. Based on the WHO DDD, it was found that Pantoprazole 20mg and Actel tablet had highest DDD with 0.12 per 1000 residents per day.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCE

[1] Sung J, Kuipers E, El-Serag H. Systematic review: the global incidence and prevalence of peptic ulcer disease. Alimentary pharmacology & therapeutics. 2009;29(9):938-46.

[2] Mary Chok Chiew Fong AIAS. MALAYSIAN STATISTICS ON MEDICINES. Malaysia: Pharmaceutical Services Programme Ministry of Health Malaysia; 2015.

[3] Goh KL. Prevalence of and risk factors for Helicobacter pylori infection in a multi-racial dyspeptic Malaysian population undergoing endoscopy. Journal of gastroenterology and hepatology. 1997;12(6):S29-S35.

[4] Chandran P, Prakasam KA, Jayachandran A, Mary A. TO ANALYSE THE RISK FACTOR AND DRUG UTILIZATION REVIEW OF PEPTIC ULCER DISEASE IN A TERTIARY CARE HOSPITAL. 2019.

[5] Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. New England Journal of Medicine. 1998;338(11):727-34.

[6] Oh AL, Tan AG, Phan HS, Lee BC, Jumaat N, Chew SP, et al. Indication of acid suppression therapy and predictors for the prophylactic use of protonpump inhibitors vs. histamine-2 receptor antagonists in a Malaysian tertiary hospital. Pharmacy practice. 2015;13(3).

[7] Raj S. Peptic ulcer disease in Kelantan: an underdiagnosed condition? The Medical journal of Malaysia. 1991;46(2):183-6.

[8] Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence. Therapeutic advances in gastroenterology. 2019;12:1756284819834511.

[9] Pendhari SR, Joshi KS, Limaye RP. Use of proton pump inhibitors–A drug utilization study. Indian J Pharm Pharmacol. 2016;3:88-94.

[10] Kandasami P, Tan W, Norain K. Gastric cancer in Malaysia: the need for early diagnosis. The Medical journal of Malaysia. 2003;58(5):758-62.

[11] Wertheimer A. The defined daily dose system (DDD) for drug utilization review. Hospital pharmacy. 1986;21(3):233-4, 9.

[12] Daniel WW, Cross CL. Biostatistics: a foundation for analysis in the health sciences: Wiley; 2018.

[13] Mustafa M, Menon J, Muiandy R, Fredie R, Sein M, Fariz A. Risk factors, diagnosis, and management of peptic ulcer disease. J Dent Med Sci. 2015;14(7):40-6.

[14] Graham DY, Malaty HM, Evans DG, Evans Jr DJ, Klein PD, Adam E. Epidemiology of Helicobacter pylori in an asymptomatic population in the United States: effect of age, race, and socioeconomic status. Gastroenterology. 1991;100(6):1495-501.

[15] Narayanan M, Reddy KM, Marsicano E. Peptic ulcer disease and Helicobacter pylori infection. Missouri medicine. 2018;115(3):219.

[16] Zhang Y-S, Li Q, He B-S, Liu R, Li Z-J. Proton pump inhibitors therapy vs H2 receptor antagonists therapy for upper gastrointestinal bleeding after endoscopy: a meta-analysis. World Journal of Gastroenterology: WJG. 2015;21(20):6341.

[17] Benmassaoud A, McDonald EG, Lee TC. Potential harms of proton pump inhibitor therapy: rare adverse effects of commonly used drugs. CMAJ. 2016;188(9):657-62.

[18] Leven C, Hudier L, Picard S, Longuet H, Lorcy N, Cam G, et al. Prospective study of drug-induced interstitial nephritis in eleven French nephrology units. Presse medicale (Paris, France: 1983). 2014;43(11):e369-76.

[19] Whitlock J. Common Medications Before, During, and After Surgery: Well Health; 2019 [Available from: https://www.verywellhealth.com/drugs-used-before-during-and-after-surgery-3156830.

[20] D'Souza AM, Shastry C, Mateti UV, Kabekkodu S, Chand S. Drug Utilization and Evaluation of Proton Pump Inhibitors in General Medicine Ward of a Tertiary Care Hospital. Journal of Pharmaceutical Sciences and Research. 2019;11(6):2174-9.

[21] McNicholl A, Linares P, Nyssen O, Calvet X, Gisbert J. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of H elicobacter pylori infection. Alimentary pharmacology & therapeutics. 2012;36(5):414-25.

[22] Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Alimentary pharmacology & therapeutics. 2005;21(6):739-46.

[23] Mathews S, Reid A, Tian C, Cai Q. An update on the use of pantoprazole as a treatment for gastroesophageal reflux disease. Clinical and experimental gastroenterology. 2010;3:11.

[24] GEORGE S, inventorOral pharmaceutical composition with delayed release of active ingredient for pantoprazole1995.

[25] Skrzydło-Radomańska B, Radwan P. Dexlansoprazole–a new-generation proton pump inhibitor. Przeglad gastroenterologiczny. 2015;10(4):191.