

Original Research Article

Prescribing Practices and Cost of Drugs for Peptic Ulcer in a Primary Health Center in Pulau Penang, Malaysia

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Abstract

Purpose: Description of the prescribing patterns of gastric acid suppressant treatment in peptic ulcer disease and the cost analysis in a tertiary health center in Malaysia

Methods: A cross sectional retrospective study was conducted at a Universiti Sans Malaysia (USM) Health Center, Clinic, Malaysia. Convenience sampling was used to include 100 peptic ulcer patients.

Results: Sixty three percent of the patients were male and 37 % female. The majority of the patients were Malay (71 %) and mean age was 46 ± 9.7 years. The most frequently prescribed monotherapy antiulcer drugs were ranitidine (83 %) and omeprazole (17 %), while for combination therapy (with antacids), it was ranitidine (85 %). The average cost of anti-ulcer drug therapy was 15.54 Ringgit Malaysian (RM), i.e., (USD 4.98) for omeprazole and RM 4.62 (USD 1.48) for ranitidine.

Conclusion: The practitioners in this study preferred to prescribe ranitidine much more frequently than omeprazole. Considering the cost burden of proton pump inhibitors (PPIs) and their relatively more adverse effects, this may be a cost-effective strategy, but the benefits of ranitidine in terms of therapeutic efficacy need to be ascertained.

Keywords: Peptic ulcer, Gastric acid suppressant, H₂ receptor antagonist, Proton pump inhibitor

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INTRODUCTION

Although a majority of studies report a decrease in the incidence or prevalence of PUD over time, it remains a common condition. The two most common causes implicated are *Helicobacter pylori* (*H. pylori*) and non-steroidal antiinflammatory drugs (NSAID) use [1]. Apart from therapy for eradication of *H. pylori* and discontinuation of NSAID when indicated, the main strategy against peptic ulcer disease (PUD) remains gastric acid suppression.

The use of proton pump inhibitors varies between gastroenterologists and primary care

physicians, although most physicians believe that proton pump inhibitors are safe, few believe that they should be available without a prescription [2]. While proton pump inhibitors are undoubtedly effective agents, studies of their prescribing pattern in practice consistently suggest overuse prior to endoscopy, use in patients who do not fit the approved criteria, and prescribing for indications in which less potent agents should have been sufficiently effective for the patient's symptoms [3]. Also, PPIs are not completely benign medications as there are a lot of associated adverse events such as increased risk of community acquired pneumonia, increased risk of *Salmonella* and *Campylobacter* infection, delayed diagnosis of gastric cancer and

reports of severe hypomagnesaemia resistant to magnesium replacement.

For Caucasian patients, PPIs are definitely a preferred option among the gastric suppressants because of proven efficacy. When treating PUD patients of Asian origin, the fact that parietal cell mass and acid secretory capacity is much less than Caucasians, allows use of much less dose with similar response. But in eastern regions the prescribing patterns for PUD remains to be ascertained. Preference of H₂ receptor blockers over proton pump inhibitors (PPIs) in Asian patients may not only be justified but also a very economical approach, given the much higher cost of PPIs as compared to H₂ blockers. In an economically constrained scenario, pharmacoeconomics of such an approach is very appealing as it would mean utilization of any savings for other health care demands.

METHODS

Setting

This study was conducted in Universiti Sans Malaysia Health Center (USM), Malaysia. USM is a primary health centre, catering to the health care needs of university staff and their dependants.

Study design

A retrospective cross-sectional study was conducted, using convenience sampling which included the first 100 patients' files with peptic ulcer. The data source of this study was gathered from the patients' record for six months, and prescriptions available at the USM health Center Clinic, Malaysia. The data collection form mainly consisted of demographic data of the patient, drug usage, drug cost and patterns of therapy.

Inclusion and exclusion criteria

Adults aged 18 years old and above with confirmed peptic ulcer were included. Peptic ulcer diagnosis was confirmed clinically, mainly by other hospitals via endoscopy. Exclusion criteria were patients < 18 years old and non-confirmed peptic ulcer patients. Prescriptions fulfilling our inclusion criteria were selected and required information was gathered using our collection form. The documentation involved: Drug usage (drug name, dose, dosage form, frequency, duration and costs), Pattern of therapy (mono- or combination) and demographic data (age, gender and race).

Statistical analysis

The data was entered into SPSS, version 13.0, software and suitable statistical tests were used to analyze the data gathered from the data collection form. Descriptive analysis was used to present the demographic data.

RESULTS

A total of 100 patients were studied of which 63 % were male and 37% were female. The majority of the patients were Malaya (71 %), Chinese were 7%, Indian 12 % and others were 12 %. Mean age of the patients was 45.94. Table 1 gives the mean duration of therapy for each drug and the mean cost. The majority of the patients were prescribed ranitidine (83%) as monotherapy (Table 2). Omeprazole was prescribed much less frequently (17%). Even as combination therapy the most frequently prescribed drug was ranitidine (85%). The average cost of drug therapy of gastric acid suppressant drugs was RM 15.54 (USD 4.98) for omeprazole as compared to just RM 4.62 (USD 1.48) for ranitidine (Table 3). Finally Table 4 gives the association of comorbidities with our PUD patients. More than half of our patients (52) had an associated comorbidity; hypertension and dyslipidemia were encountered most frequently. Forty eight of our patients did not have an associated comorbidity and presented only for treatment of PUD (Table 4).

Table 1: Mean duration of therapy (n = 100)

Parameter	Mean ± sd
Duration of omeprazole (days)	31.24±11.30
Duration of ranitidine (days)	20.75±12.60
Duration of Actal (days)	6.33±4.90
Duration of Zellox (days)	9.13±8.340
Cost of therapy (RM/day)	6.79±5.79
	(USD 2.18±1.86)
Number of visits (days)	1.53±1.08

Zellox[®] composition: aluminum hydroxide
magnesium hydroxide simethicone

Actal[®] composition: sodium polyhydroxyaluminium
monocarbonate hexitol complex

DISCUSSION

In the present study, the most frequent antiulcer drugs used as monotherapy and combination therapy were H₂-receptor inhibitors (H₂RAs, 83 - 85 %), PPIs were the less frequently used antiulcer drugs as monotherapy as well as in combination therapy (17 - 14 %). Thus, in our study, H₂RAs were much more preferred to PPIs.

Table 2: Distribution of antiulcer drugs utilized by the patients (n=100)

Mode of therapy	N	%
Monotherapy	65	65
Combination therapy	35	35

Most frequent antiulcer drugs as monotherapy

Ranitidine	54	83
Omeprazole	11	17
Actal	0	0
Zellox	0	0

Most frequent antiulcer drugs as combination therapy

Ranitidine +actal	18	51.4
Ranitidine +zellox	12	34.3
omeprazole +actal	3	8.6
omeprazole +zellox	2	5.7

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Table 3: Average cost of drug therapy of antiulcer drugs

Antiulcer drug	Average cost drug therapy in Ringgit Malaysian (USD)
Omeprazole	15.54(4.98)
Ranitidine	4.62(1.48)
Actal	0.92(0.29)
Zellox	2.19(0.70)

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Gastric acid suppressant therapy in the form of an H2 blocker or proton pump inhibitor for four weeks induces healing in most duodenal ulcers. Proton pump inhibitors provide superior acid suppression, healing rates, and symptom relief and are recommended as initial therapy for most patients. One meta-analysis of randomized controlled trials comparing proton pump inhibitors with H2 blockers showed earlier pain control and better healing rates at four weeks for proton pump inhibitors (85 versus 75 %) [4]. Another systematic review of randomized controlled trials showed that proton pump inhibitors healed duodenal ulcers in more than 95 % of patients at four weeks and gastric ulcers in 80 to 90 percent of patients at eight weeks [5]. PPIs are more effective than H2RA in preventing persistent or recurrent bleeding from peptic ulcer, although

this advantage seems to be more evident in patients not having adjunct sclerosis therapy. However, proton pump inhibitors are not more effective than H2RA for reducing surgery or mortality rates [6].

Table 4: Co-morbidities associated with peptic ulcer disease (n = 100)

Co-morbidities	N	%
	8	8
Hyperlipidemia	7	7
Hemorrhoids	4	4
Ischemic heart disease	4	4
Gout	2	2
Tendinitis	2	2
Diabetes	2	2
Hypertension + Diabetes	5	5
Hypertension +hyperlipidemia	5	5
Diabetes +Hyperlipidemia	3	3
Gout+ischemic heart dis.	2	2
Hypertension + Diabetes +Hyperlipidemia	4	4
Hypertension +Ischemic+hyperlipidemia.	1	1
Hypertension + Diabetes +gout+ hyperlipidemia.	2	2
Peptic Ulcer alone	48	48

Recommendations of the majority of guidelines and reviews recommend PPI as first line for eradication therapy in PUD. Though the superiority of PPIs is proven in Western literature, it has not been studied in Asian populations. The parietal cell mass of Scottish patients with duodenal ulcer has been shown to be almost double that of Chinese patients, yet peptic ulcer occurs in about 10 % in both populations. The gastric acid output following maximal stimulation is known to be higher in western patients and controls than in their Asian counterparts, by as much as 80 %. There are two known explanations. First, body weight has been shown to be closely related to maximal acid output, and body size in Asians is generally less than that in Caucasians. However, despite correction for body stature, Chinese still showed a significantly smaller maximal acid output compared with age- and sex-matched. Parietal cell counts and maximal acid output in Chinese and Scottish patients with duodenal ulcer. Another explanation may be related to H. pylori gastritis, which is common among Asians and which may reduce the acid secretion, especially when the body and fundus are involved.

The parietal cell mass is much less in Asians [7]. The fact that acid secretion in Asians is only

about 60 % of that in Caucasians is of importance when treating Asian patients with acid-reducing agents [8]. Identical suppression of acid secretion induced by graded doses of pentagastrin, has been shown with cimetidine 100 mg and 200 mg intravenously, in Chinese patients with duodenal ulcer, suggesting that half the standard dose of cimetidine that is recommended for Caucasians might achieve adequate acid suppression in Chinese; this has, in fact, been reiterated by a double-blind, placebo-controlled study showing that cimetidine 100 mg and 200 mg was as effective as 200 mg three times daily and 400 mg for the healing of duodenal ulcer[9,10]. Thus the preference of H2RAs to PPIs in the present study may thus be justified keeping in view the difference in acid secretion as well as response to gastric acid suppressants in Asian population.

Even in Western literature, there is a wide variation in amount of PPIs used by the GPs, a multifold difference between the highest and lowest users. It was found that a significantly large percentage of patients were being prescribed proton pump inhibitors for the unlicensed indications of non-ulcer dyspepsia and nonspecific abdominal pain. In 1998, there were 2 million prescriptions for proton pump inhibitors dispensed throughout Australian community pharmacies, at a cost to government of approximately Australian \$180 million; omeprazole was the second most costly Pharmaceutical Benefits Scheme item for that year. Total PPIs prescribing increased yearly in some studies, between 1990 and 1996; while the prescription of proton pump inhibitors rapidly increased, the use of H₂-antagonists did not decrease greatly. There is thus a wide variation in use of PPIs and a scope for improvement [11]. In the west there has been a decline in use of H2RAs and a multifold increase in prescriptions of PPIs [12].

Moreover, our study also demonstrates that there is a major difference in the cost of therapy (The average cost of drug therapy of gastric acid suppressant drugs was 15.54 RM(4.98USD) for omeprazole as compared to just 4.62 RM(1.48 USD) for ranitidine). Thus H2RAs have a definite advantage over PPIs from economic point of view, especially in developing nations. When we look at the co-morbidities, we find that more than half the patients of PUD have an associated co-morbidity for which they would require treatment. This obviously increases the total cost of the prescription and thus it is all the more important to look for means for lessening the economic burden of disease, like was the case in our study,

wherein preference of H2RAs meant a definite reduction in the total cost.

While the proton pump inhibitors are no doubt effective agents, and studies to be imposed on the ground indicate consistently excessive use before endoscopy, use in patients who do not fit the criteria, and description of the indicators that agents' less powerful "should be effective, including enough to the symptoms of the patient.

Over utilization of proton pump inhibitors without an adequate trial of H₂-antagonists. The cost-effectiveness of such changes in prescribing remains unclear. Concern has been expressed that many patients may be treated with these expensive drugs without having tried life-style modification or simpler, less expensive treatments.

Though PPIs are now among the most commonly prescribed medications worldwide, they are not entirely innocuous. A large number of patients - as many as 90% in one study [13] - are taking these drugs with no appropriate guideline-based indications. This raises fears of an economic and safety, particularly in light of the suggestion that these drugs may delay the diagnosis of gastric cancer [14]. Taking a proton pump inhibitor may allow patients to continue an unhealthy life-style which may be detrimental for their heart as well as their heartburn. Found that a significantly large percentage of patients were being prescribed proton pump inhibitors for the unlicensed indications of non ulcer dyspepsia and nonspecific abdominal pain. Several studies have shown that current PPI use, particularly if started recently, is associated with an increased risk of Community acquired pneumonia[15]. The studies did not consistently observe an association with H2RAs, perhaps because of their weaker acid suppressant activity. One study examining cardiothoracic surgery patients taking stress ulcer prophylaxis found pantoprazole, but not ranitidine, was associated with an increased risk of hospital-acquired pneumonia[16]. It has been suggested that losing the non-specific defense of a gastric pH below 4 results in more gut flora residing in the upper gastrointestinal tract, and the more powerful acid suppressant effects of PPIs would therefore be expected to be more strongly linked with pneumonia, as is observed.

There is also a significant body of observational evidence linking gastric acid suppression to enteric infection. A systematic review published in 2007[17] reported an increased risk of Salmonella and Campylobacter infection in those using gastric acid suppressants. The association

was greater with PPIs than H2RAs, but remained significant for H2RAs. Gastric acid suppression is associated with colonization of the normally sterile upper GI tract; acid suppression may therefore remove an important physiological barrier, allowing orally ingested enteric pathogens to reach the gut.

Perhaps most importantly for older people, acid suppression may also be associated with an increased risk of *Clostridium difficile*-associated disease (CDAD). Although some studies did not find an association between PPIs and CDAD, a number of other studies have demonstrated that PPI use increases the risk of developing CDAD in both hospitalised and community-dwelling patients, with a meta-analysis reporting a significant increase in risk the association for H2RA use appears to be weaker. Patients treated for CDAD are more likely to have a recurrence if they remain on PPI therapy [18].

There are other potentially adverse effects of gastric acid suppressants that are relevant to the health of older people. A number of case reports have suggested a relationship between PPIs and microscopic colitis, a condition now increasingly recognised as a cause of chronic watery diarrhoea in older people. Severe hypomagnesaemia resistant to magnesium replacement but resolving on withdrawal of PPI has been reported, especially in older people [19]. This can be partially corrected by high-dose oral magnesium supplement, suggesting that PPIs inhibit the active transport mechanism of intestinal magnesium absorption. Low serum magnesium levels have been shown to be associated with adverse prognosis and increased mortality in various settings and have been found to independently correlate with muscle performance in older people.

The change in gastric acidity with consequent changes in drug absorption has been blamed for malabsorption of nutrients including iron, vitamin B12 and many of the drug interactions with PPIs. Although this has not been of major clinical concern, the recent controversy surrounding concomitant use of PPIs and clopidogrel serves as a reminder that this class of drugs is not without the risk of interactions. Finally, some recent studies have suggested an association between PPI use and increased risk of osteoporotic fracture, although this association does not appear to be consistent across all populations. There is no doubt that gastric acid suppressants are important drugs with a crucial role in the management of a number of GI diseases, and care is needed to ensure that patients taking these agents for good indications

do not have their prescriptions stopped. However, there is good evidence that they are frequently being prescribed for non-specific and inappropriate reasons, and that a large number of patients are taking these agents for much longer than necessary.

CONCLUSION

The majority of patients of PUD in this study were on ranitidine, while only few others were placed on omeprazole. Thus, H₂RAs were clearly the preferred gastric acid suppressants in this study population. The rationale for this prescribing pattern is probably a reduction in cost burden, adverse event profile of PPIs and consideration of PPIs for only recurrent cases when H₂ antagonists fail. What remains to be ascertained is the therapeutic effectiveness of H2RAs over PPIs in Asian patients with PUD.

Limitations of the study

Study population is limited to only a single centre in Penang, Malaysia and looks only into the prescribing pattern in PUD. Further prospective studies are required to find and compare the response of H2blockers and PPIs in PUD in Malaysian patients.

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