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Research paper

Reducing the cost of proton pump inhibitors by adopting best practice

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ABSTRACT

Objectives To evaluate the appropriateness of proton pump inhibitor (PPI) use by assessing the level of compliance of PPI prescribing practices with published guidelines and to assess the potential cost avoidance through inappropriate prescribing.

Method A six-week observational study of PPI prescriptions was undertaken between April and June 2005, involving hospital inpatients who were taking a PPI prior to admission. The patients were evaluated using a standardised questionnaire to obtain information regarding their PPI use and efficacy.

Results Among the 679 patients admitted during the study period, 133 were receiving a PPI, and of these 97 (50 men and 47 women) were enrolled into the study. The commonest indication for PPI use was gastro-oesophageal reflux disease (GORD, $n = 71$; 73.2%). In this cohort, more than one-quarter of patients (26.6%) were using greater than the standard PPI dose. Over half of the patients had at least one risk factor known to exacerbate GORD (51.5% were overweight, 46.4% alcohol consumers and 14% current smokers), and 71.1% were receiving medications known to cause or worsen reflux symptoms. Of those patients who reported alarm symptoms, 84% had undergone endoscopy. The overall compliance with the Pharmaceutical Benefits Scheme (PBS) prescribing guidelines was 78.4%, with the major reason for non-compliance being use for non-PBS indications. Estimated cost savings through adoption of recommended prescribing practices and the implementation of step-down therapy for GORD patients were up to AUD 90 866 and AUD 118 456 per 100 patient-treatment-years, respectively.

Conclusion PPIs continue to be prescribed outside the treatment guidelines. As a result, opportunities exist to reduce the cost of PPI use through management of contributing factors, adherence to recommended dosage schedules and use of step-down therapy in asymptomatic patients where appropriate.

Keywords: gastro-oesophageal reflux, guidelines, proton pump inhibitors, step-down therapy

How this fits in with quality in primary care

What do we know?

PPIs are widely used for the management of acid-related gastrointestinal disorders and non-steroidal anti-inflammatory drug (NSAID)-induced gastrointestinal lesions, contributing significantly to healthcare costs. When used in accordance with treatment guidelines they are highly effective and generally safe, although evidence is emerging that long-term use may result in vitamin B_{12} malabsorption, an increase in hip fracture risk, and risk of infectious gastroenteritis and *C difficile* infection.

What does this paper add?

Compliance with prescribing guidelines remains an issue, in particular the failure to use step-down therapy in patients with asymptomatic GORD, which has significant cost implications. There is a need for a systematic approach to the use of PPIs, including addressing lifestyle and medication factors contributing to patients' symptoms, adherence to recommended treatment guidelines and regular review to facilitate step-down therapy.

Introduction

Since proton pump inhibitors (PPIs) were introduced into clinical practice in the 1980s, they have become the drugs of choice for management of acid-related gastrointestinal (GI) disorders.[1] Moreover, they generally appear to be safe and more effective than the histamine-2 receptor antagonists (H_2RAs) in acid-suppressing activity, controlling symptoms and producing healing.[1–4] There are currently five PPIs available in Australia – omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole.

Apart from their proven efficacy, PPIs have been shown to be safe and well tolerated.[1,2] The most commonly reported adverse effects (incidence 1–3%) are nausea, headache, diarrhoea, constipation and skin rash.[1,2] Although there is ample evidence to indicate that PPIs have an excellent short-term adverse effect profile, their long-term adverse effects in humans has been less extensively studied. The main concerns with PPIs include their long-term adverse effects of profound acid suppression leading to hypergastrinaemia, development of gastric enterochromaffin-like (ECL) cell hyperplasia, gastric bacterial overgrowth, and alteration of nutrient absorption.[5,6]

In the past decade, the use of PPIs has increased rapidly. Likewise, expenditure on these agents has increased dramatically. In Australia, the number of PPI prescriptions dispensed through the Pharmaceutical Benefits Scheme (PBS) has rapidly increased from 0.7 million in 1995 to over 11 million in 2004. As a consequence, the cost of PPIs to the Australian government has increased substantially from Australian dollars (AUD) 66 million in 1995 to approximately AUD 500 million in 2004.[7] In 2006, there were three PPIs (esomeprazole AUD 208 million, omeprazole AUD 158 million and pantroprazole AUD 119 million) among the top ten drugs on the PBS by expenditure.[8] This upward trend of PPI use is not unique to Australia but has been documented worldwide.[9–11] Therefore, there has been continued pressure to restrict the use of PPIs, especially in long-term administration, through either mandatory restrictions or incentive programmes to minimise PPI dosage, frequency, and duration of treatment. In Australia, restrictions on the PBS through which PPI supply is subsidised by the government is a key strategy to control use in the primary care setting, as are the publication of national prescribing guidelines. Despite such measures, inappropriate use of PPIs remains a problem, as highlighted in several studies.[12–15] This includes the use of PPIs for unapproved indications, use of too high a PPI dosage, and inadequate use of less expensive agents or investigations prior to commencing PPIs. Furthermore, it has been found that using drugs that are known to cause or exacerbate gastro-oesophageal reflux disease (GORD) such as calcium channel blockers is associated with an increased use of PPIs,[16] and such use should be addressed before using PPIs.

Identifying and correcting inappropriate prescribing is a key strategy in reducing the cost of drug use, which has the potential to contribute to substantial savings for the healthcare system. This study aimed to evaluate the appropriateness of use of PPIs by assessing the level of compliance with PBS indications,[17] and recommendations contained within the *Therapeutic Guidelines: Gastrointestinal* (2000),[18] as well as the potential cost avoidance through either drug cessation or dosage change.

Method

An observational study was performed on eligible patients admitted to four wards (two general medical and two general surgical wards) at Sir Charles Gairdner Hospital, a teaching hospital in Western Australia, during the period April 2005 to June 2005. Patients who were admitted on a PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole or esomeprazole) were consecutively recruited. Only patients who did not wish to participate in the study or who could not communicate in English were excluded from the study. Eligible patients were identified by review of their admission medications by the primary researcher. After giving written informed consent, they were then interviewed by the primary researcher, using a standard questionnaire to determine the indication, dose and duration of PPI use; investigations undertaken to diagnose their GI disease, concurrent use of medications that are known to cause or exacerbate GORD, and response to PPI therapy, together with social (alcohol and tobacco use) and demographic data.

The level of appropriateness of PPI use was evaluated by assessing the level of compliance with the PBS schedules at the time of the study,[17] and the *Therapeutic Guidelines: Gastrointestinal* (2000), which are the accepted management guidelines in Australia.[18]

Statistical analyses were performed by using the Windows-based Statistical Package of the Social Sciences (SPSS) Version 13.0. Data obtained from the questionnaires were coded and entered into an SPSS database. Data entries were checked upon completion against the original questionnaires. A standard significance level of $P < 0.05$ was considered statistically significant.

Data analysis was divided into two parts: evaluation of level of compliance with guidelines and assessment of estimated cost avoidance.

Appropriateness of the use of proton pump inhibitors

Compliance of PPIs prescription with PBS schedules,[17] and the recommendations contained within the Therapeutic Guidelines: Gastrointestinal (2000)[18]

- The percentage of patients who received proton pump inhibitors who met PBS criteria (indication and dosage) was calculated.
- Reasons for not satisfying the criteria were identified.

Clinical investigations and other therapies before commencing PPIs

- The percentage of patients who had investigations (e.g. endoscopy or barium meal) prior to the commencement of their PPI was calculated.
- The percentage of patients who had previously used an H_2RA and/or antacid was calculated.

Presence of risk factors or the concurrent use of drugs that are known to cause or exacerbate upper GI condition (comprehensive list derived from the literature)

- The percentage of patients who had risk factors or were concurrently using such medications were calculated.

Cost-avoidance assessment

Cost avoidance (or cost of over-utilisation) of PPIs included the following calculations:

- cost of PPIs use outside PBS criteria
- cost savings if step-down therapy was applied to GORD patients who were asymptomatic
- cost difference between cost of PPIs used without investigation (empirical therapy) and the cost of therapy with investigation.

For the purpose of analysis, the cost of the PPIs represented the PBS price, and the cost of endoscopy the Medical Benefits Scheme schedule price. All costs were expressed as AUDs saved per 100 patient-years of PPI use.

For the purpose of the study, the 'standard' dose was defined as single daily dosing of a PPI and in the following doses – omeprazole 20 mg, lansoprazole 30 mg, pantroprazole 40 mg, esomeprazole 20 mg and rabeprazole 20 mg.[18] The options for step-down therapy for GORD used in the cost-avoidance analysis were reduction in PPI maintenance dose (double to standard, standard to half, on-demand daily dosing), change to a regular standard-dose H_2RA, or no treatment. The average cost for standard-dose PPI per year used was AUD 615.17, and standard-dose H_2RA AUD 280.41. The Medicare rebate for an endoscopy was AUD 127.80.

Results

During the six-week study period, there were 679 patients admitted to the four wards. Of these, approximately one-fifth (133 patients) were identified as receiving a PPI before admission, of whom 97 patients were recruited into the study. The remaining 36 were excluded because they could not speak English (6), had mental or physical impairment (17), were unable to answer the questions (6), or were unwilling to participate (7). There were slightly fewer females (47; 48.5%) than males in the group (50; 51.5%). The mean age of patients was 66 ± 14.3 years, with no significant difference between males and females.

Omeprazole was the most frequently prescribed PPI (39; 40.2%) in the study patients, followed by esomeprazole (29; 29.9%), pantoprazole (15; 15.5%), lansoprazole and rabeprazole (both 7; 7.2%). GORD was the most common indication for PPI use (see Table 1).

Table 1 Clinical indications for prescribing proton pump inhibitors

Indication	Number (%)
Gastro-oesophageal reflux disease	71 (73.2)
Peptic ulcer disease	18 (18.5)
Prophylaxis of drug-induced ulcers	10 (10.3)
Upper gastrointestinal bleeding	4 (4.1)
Scleroderma oesophagus	3 (3.1)
Uninvestigated dyspepsia	2 (2.1)
Eradication of *H. pylori*	1 (1.0)
Indigestion	1 (1.0)
Oesophageal diverticulosis	1 (1.0)
Ulcers associated with nasogastric tube	1 (1.0)
Gastric antral vascular ectasia	1 (1.0)
Unknown/not documented	2 (2.1)
Total	115 (118.4[a])

The median duration of PPI therapy for patients in the study was two years, with a minimum of 10 days, for a patient prescribed a PPI for acute upper GI bleeding, and a maximum of 20 years, for a patient with GORD. Over half the patients (54; 57.4%) were prescribed a standard dose PPI, whereas 26.6% were taking double (23; 24.5%) the standard dose or more (2; 2.1%), and 16.0% were using half dose. Sixty-two patients (63.9%) had had at least one investigation for their GI symptoms before commencing their PPI, with 42 of 50 patients (84%) who reported alarm symptoms having undergone endoscopy. Barium swallow and meal was done in almost half of patients (48.5%). Twenty-seven patients (27.8%) had been tested for *H. pylori*, with 10 (37.0%) reporting a positive result, 14 (51.9%) a negative result, and three (11.1%) unable to recall the outcome of the test. Eighty-six (88.7%) patients stated that they had tried an antacid and/or H_2RA before being initiated on a PPI. However, only 27.9% were satisfied with the effectiveness of previous agents on their symptoms.

Factors known to exacerbate upper GI conditions were evaluated. Approximately 14% (13) of the patients were current smokers, nearly half (45; 46.4%) were current drinkers, and just over half (50; 51.5%) were considered to be overweight based on a body mass index (BMI) > 25 kg/m^2. The use of at least one medication known to cause or worsen gastro-oesophageal disorders, either by direct irritation of the gastrointestinal tract or relaxing the lower oesophageal sphincter (LOS), was documented in 69 (71.1%) of the patients. Aspirin was the most commonly prescribed medication known to precipitate gastro-oesophageal symptoms, with 24 (24.7%) patients receiving this drug, followed by calcium channel blockers (20; 20.6%), bisphosphonates (19; 19.6%), and non-steroidal anti-inflammatory drugs (NSAIDs) (18; 18.6%). The patient interviews revealed that nearly half (43.3%) of these medications had been commenced prior to patients starting PPI therapy.

The level of compliance of PPI prescribing with the PBS requirements and the *Therapeutic Guidelines: Gastrointestinal* (2000) (see Table 2) was also determined. The overall compliance with the prescribing guidelines (PBS and *Therapeutic Guidelines: gastrointestinal* (2000)) was 78.4%. Reasons for not satisfying the guidelines were use for non-PBS subsidised indications (in 16.5% of cases), use of a PPI that was not subsidised for a specific indication (2.1%), use in patients who did not fulfil the prescribing criteria (2.1%), and using a higher than recommended dose of a PPI (1.0%), as shown in Figure 1.

The potential for cost savings through addressing inappropriate prescribing, and the use of step-down therapy were investigated. Estimated cost avoidance

Table 2 Non-subsidised and subsidised indications for PPI therapy by the PBS

Unsubsidised indication	Subsidised indication
Maintenance treatment of peptic ulcer disease	Gastro-oesophageal reflux disease
Upper gastrointestinal bleeding	Scleroderma oesophagus
Uninvestigated dyspepsia	Eradication of *H. pylori*
Indigestion	
Oesophageal diverticulosis	
Ulcers associated with nasogastric tube	
Gastric antral vascular ectasia	
Unknown/not documented	
Prophylaxis of drug-induced ulcers[a]	

[a] Recommended by the Therapeutic Guidelines: gastrointestinal (2000)

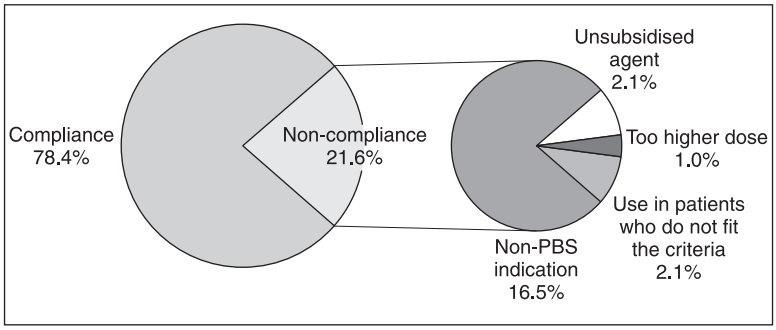

Figure 1 Overall compliance between use of PPIs and prescribing guidelines

for PPI use outside the guidelines including the cost of PPI use for non-PBS-subsidised indications, and cost-saving through implementation of recommended treatment regimens was estimated to be between AUD 58 938 and 90 866 per 100 patient-treatment-years.

There were 58 patients who had uncomplicated GORD (i.e. patients who did not report severe erosions, scleroderma, stricture or Barrett's oesophagus), and of these 45 were eligible for step-down therapy based on the absence of ongoing GORD symptoms. Assessment of potential cost avoidance in these patients was divided into two groups; in patients who were on double (high)-dose PPI and in patients who were on standard-dose PPI. Potential cost saving of AUD 55 294 per 100 patient-treatment-years was calculated based on reduction to standard dose in patients whose symptoms were controlled with a double-dose PPI. This saving then was added to potential savings from four different strategies of step-down therapy in those who were on standard-dose PPI, to obtain a range for potential savings (half-dose PPI AUD 23 818, intermittent PPI therapy AUD 48 423, maintenance H_2RA AUD 35 121, and no treatment AUD 63 162 per 100 patient-treatment-years). The potential cost saving if step-down therapy was implemented in patients with asymptomatic uncomplicated GORD initially on a double-dose PPI with a success rate of 100% were estimated to range between AUD 23 818 (standard to half-dose PPI) and AUD 118 456 (double-dose PPI to no treatment) per 100 patient-treatment-years (see Figure 2). The actual savings would of course be dependent on symptom control and patients' preference for step-down treatment. However, given that there were one million PBS prescriptions written per month in 2004–2005,[19] which is equivalent to one million patient years of treatment (generally one prescription equals one month's supply), and the majority of these were for the treatment of reflux, there is potential to save of hundreds of millions of Australian dollars.

Finally, the estimated cost avoidance for PPI therapy in patients who received a PPI for uninvestigated indications if endoscopy had been performed and revealed no indication for a PPI, was AUD 57 906 per 100 patient-treatment-years.

Discussion

The pattern of prescribing of PPI observed in the sample was similar to that seen in data obtained from the Health Insurance Commission (HIC), which represents the pattern of PPI prescribing through PBS in Australia.[7]

Several early studies demonstrated the use of PPIs outside recommended guidelines in Australia.[12–15] McManus and colleagues conducted a cohort study in 1996 to evaluate compliance in the use of PPIs with subsidised indications listed by the PBS in 4554 new PPI users in Australia.[12] The results of the study demonstrated that there was widespread use of PPIs outside subsidised indications, particularly use in less severe forms of oesophageal disease. A review of omeprazole use in one hospital in Hobart showed that half the omeprazole prescribed did not satisfy the hospital requirement for an initial trial of an H_2RA.[13] A subsequent study conducted in the same hospital showed a similar result, with only 37% of PPI use satisfying the approved indications as outlined in the PBS.[14] Pillans and others reported that only 22.5% of the use of PPIs in a hospital in Queensland satisfied the PBS criteria.[15] The reasons for not satisfying the criteria included the use of PPIs in milder forms of GORD, and no adequate trial of H_2RA therapy before prescribing a PPI. Similar

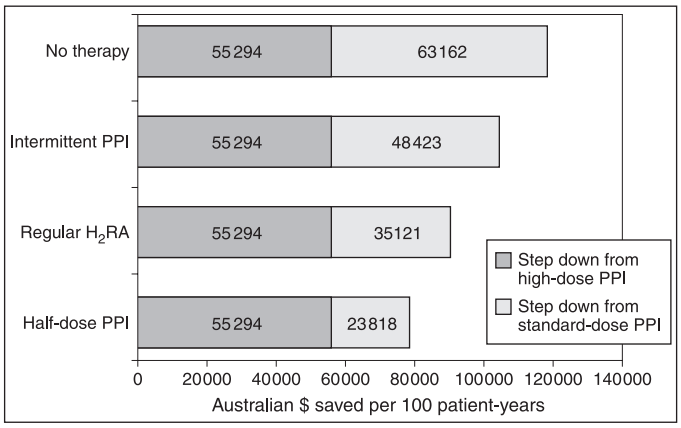

Figure 2 Potential savings by step-down therapy in GORD patients who were asymptomatic assuming 100% successful rate

Note: Total potential saving is calculated based on the sum of the potential savings from stepping down from high (double) dose PPI to standard dose PPI, then standard dose PPI to either half dose, intermittent PPI, regular H_2RA or no treatment.

findings of PPI overuse were also reported internationally.[7,8]

A higher level of compliance with guideline recommendations was observed in this study than in previous mentioned studies. Approximately 78% of PPI use in this study satisfied the guidelines, whereas the level was 22–51% in previous studies.[12–14] This may in part be due to the amendments to the PBS indications and the recommendations contained within the *Therapeutic Guidelines: Gastrointestinal* (2000), allowing short-term PPI use in every GORD patient regardless of the disease severity.[17,18] New guidelines suggest that patients who are commenced on a PPI should be stepped down to a less potent agent once symptoms are controlled. This management strategy of GORD is called the 'step-down' approach, which has been changed from the past where a 'step-up' approach was recommended.[20]

In 2004–2005, it was reported that 75% of patients presenting for the first time with reflux symptoms to their general practitioner (GP) in Australia received a prescription for a PPI.[19] At that time the volume of PPI prescriptions on the PBS was around one million per month.[19] PPIs are now accepted as first-line treatment for GORD,[1,2,18] so the above findings were not unexpected. Still, the National Prescribing Service (NPS) in Australia in 2006 ran a campaign to raise GPs' awareness of current best practice of the management of GORD and uninvestigated dyspepsia, including step-down therapy. This was driven by evidence that two-thirds of PPI prescriptions were for maximum repeats, and only 1 in 10 was for a lower-dose preparation, suggesting under-utilisation of step-down therapy.

This study shows that almost 90% of patients stated trying an antacid and/or H_2RA before initiating a PPI, and 71.1% of patients were using medications that are known to cause or exacerbate GORD (including aspirin, NSAIDs, bisphosphonates and calcium channel blockers). Similar findings have been reported by Naunton and his colleagues in Tasmania,[14] who reported that 59% of patients had previously been prescribed H_2RAs before commencing PPIs, and 67.5% of patients were taking drugs that are known to cause or exacerbate GORD. Withdrawal of such problem drugs should be attempted where possible, as this may alleviate the need for acid-suppression therapy. Similarly, action should be taken to address predisposing factors including excessive weight, and alcohol and tobacco intake. This study found many PPI recipients had lifestyle factors that could contribute to their GI symptoms.

There were several limitations to this study that we acknowledge. Firstly, the study was undertaken in 2005, and there may have been changes in practice since that time, particularly after the NPS campaign in 2006. Secondly, not all of the data used in the study could be confirmed with objective evidence from the patient's medical record or endoscopy report, as some patients had their investigations done outside the hospital. In such cases, these data were derived solely from patient interview, which may not have been reliable. Thirdly, cost-avoidance analysis was based on an assumption that all of the GORD patients who reported being asymptomatic on their current dose of PPIs could be successfully stepped down to less-expensive regimens, and that all patients would be willing to participate in step-down therapy, whereas, implementation of step-down therapy is influenced by patient preference. Further studies are needed to determine the success of step-down therapy to allow more precise cost-saving estimations. Fourthly, the cost of upper GI endoscopy used was the Medicare rebate, which does not take into account all costs associated with the procedure, such as accommodation costs and costs of medical follow-up, these costs are now estimated to total around AUD900 (personal communication). Therefore, cost avoidance may have been over-estimated in this study. Lastly, the small number of subjects in the study may limit the estimated cost saving of PPI therapy, and the low numbers of patients who did not have investigations prior to commencing a PPI may limit generalisation of the findings to the wider population. Furthermore, in the absence of alarm symptoms, empirical use of PPIs in patients with dyspepsia is now considered acceptable.

In conclusion, PPI prescribing appeared less than optimal when compared with the PBS and *Therapeutic Guidelines: Gastrointestinal* (2000). Opportunities exist to reduce the cost of PPI use through management of contributing factors, adherence to recommended dosage schedules and use of step-down therapy in asymptomatic patients with GORD where appropriate.

ETHICS APPROVAL

The study was approved by the Curtin University of Technology Human Research Ethics Committee and the Sir Charles Gairdner Hospital Ethics Committee.

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PEER REVIEW

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CONFLICTS OF INTEREST

None.

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