RISING USE OF PROTON PUMP INHIBITORS: A KARACHI PERSPECTIVE

Syed Hasan Abbas Naqvi[1],Syed Mohammad Saqib [2]
Waleed Ahmad Khan [3], Iftikhar Ahmad Asim Syed[*]
[1] HSE, Ireland, [2,3] Fatima Hospital, BMU, Karachi
*corresponding author, Department of Medicine, BAQAI Medical University, Karachi,
email:asimsyed01@hotmail.com

ABSTRACT: *The use of Proton pump inhibitors (PPIs) is constantly on increase, both in primary care as well as secondary care for more than 25 years. With increasing prescription, there are growing concerns about their significant adverse effects. Using a structured proforma, a cross-sectional survey of appropriateness of PPI prescription was conducted among our inpatient population, admitted from 1st Feb to 1st March 2014. This study was aimed to assess the extent of PPI prescriptions in primary and in secondary care also. We also noted the indications as well as duration of PPI use.*

There were total 288 patients admitted during our survey period. Patients were interviewed on their discharge so that we had their discharge prescription as well. 136 out of 288 patients had PPIs on discharge prescription, 104 were already taking PPIs on admission from their primary care out of which in 12 cases PPIs were discontinued during their hospital stay, while 44 were commenced in Fatima Hospital.

Our results suggest that PPIs are over prescribed in primary as well as secondary care setting. There is scope towards more careful and cost-effective PPI prescribing which can improve adherence to evidence based practice and reduce the long term adverse effects of PPIs.

INTRODUCTION

All antisecretory drugs including Histamine 2 receptor antagonists and PPIs have revolutionized the treatment and outcome of acid peptic disease. They are generally considered safe and cost effective treatment for acid peptic disease but recent studies have raised concerns about their safety in long term use. There is an increasing trend towards use of PPIs during last two decades in both hospital and primary care settings despite rising concerns regarding clinical appropriateness of their prescription, financial implications and complications of their long term use. Reducing the inappropriate prescription of PPIs is not only a means to reduce drug costs but also an important step towards preventing PPI related adverse effects. The purpose of this study was to assess the extent and appropriateness of PPI prescribing practices in primary as well as secondary care setting.

METHODS

The study was conducted in Fatima Hospital, Baqai Medical University, a 500 bed hospital located about 24 km from biggest metropolitan of Pakistan; Karachi. The hospital caters mixed urban and rural population in suburb of Karachi city. All medical admissions in three medical wards and ICU were included during the study period. A structured pro forma was used for this study and all patients were interviewed when they have their discharge prescriptions in hand, their clinical notes were also reviewed to extract information about their past medical and drug history. The pro forma included details of patient's age, sex, specialty of admission, indication of PPI therapy, name, dose, and route of therapy, (orally vs. intravenous), origin of prescription and other prescribed medications of significance. Informed consent was obtained from patients interviewed about their PPI prescription.

INDICATIONS OF PPI THERAPY

The clinical indications considered appropriate for PPI therapy were those published in NICE guidelines 2004 are as follows,[1]

1. Patients with uninvestigated dyspepsia may be treated empirically with full dose PPI therapy for one month.
2. Patients with GORD may receive full dose PPI for 1 to 2 months.
3. Patients with oesophageal stricture following dilatation.
4. Patients with documented duodenal or gastric ulcer should be tested for H pylori and treated with PPIs and antibiotics if positive.
5. Patients who are H-pylori negative but symptomatic may be treated with PPIs for symptomatic control.
6. Co-treatment with PPIs should be offered to patients who are taking NSAIDs/ Aspirin, stopping which would have poor impact on patients health.
7. Low dose PPIs for non ulcer dyspepsia and in patients with treated H-pylori and those whose symptoms persist or recur following initial treatment.
8. Those who have intermittent symptoms should be offered PPIs on as required basis.
9. All patients should be reviewed and lowest possible dose should be offered.

RESULTS

There were 288 patients admitted during the study period of whom 160 (55.5%) were female and 128 (44.4%) were males. Among all patients 136 (47.2%) were receiving PPIs at discharge, 34 (11.8%) were taking prokinetics and 22 (7.63%) were on antacids. One hundred and four (36.11%) patients were taking PPIs when presented to Fatima hospital, 83 (79.8%) by local GPs and 7 (6.7%) patients were prescribed by another secondary care hospital, in rest of 14 patients source of prescription was not traceable. In 12 out of 104 (11.5%) patients PPIs were stopped during their hospital stay as there was no reason found for their use, Where as in

44 (15.27%) patients PPIs were initiated as inpatient, making a total of 136.

Epigastric pain +/- bloating was the indication in 49 (47.1%) out of 104 cases, retrosternal burning in 12 patients, dysphagia in 5 cases. In rest of 38 (36.5%) cases there was no clear cut indication for use of PPIs. In 23 out of 44 inpatients PPIs were initiated to protect stomach from NSAIDs and steroids, rest had diagnosis of acid peptic disease or GERD on admission.

Among 104 patients who were already taking PPIs on admission, duration was variable from 0ne week to more than 2 years. Another significant finding was that in 76% of prescription the duration was not specified and in 43% dose was higher than recommended.

Intravenous PPIs were given to 86 patients on admission for variable duration of one to 5 days, only 19 (22.9%) of them had a valid indication for iv use, ie (1) Persistant vomiting, unable to take oral medicine in 6 cases, (2) Haemetemesis in 3 cases and (3) Severe epigastric pain and retrosternal burning and previously diagnosed peptic ulcer disease in 10 cases.

Intravenous PPIs were given in 86 out of 288 patients, of them 19 (22.9%) patients were justified for receiving intravenous PPI therapy. In 65 patients (75.5%) use of IV PPIs was considered inappropriate. They did not meet criteria either for indication, dose, frequency or duration of PPIs use. Slattery et al. found that intravenous proton pump inhibitors use in hospital practice is usually inappropriate most of them being treated for ulcer prophylaxis, presumed gastrointestinal haemorrhage, unrelated gastrointestinal conditions or for unknown reasons[2]. In another study only 50% of patients were receiving IV PPI for an appropriate indication[3].

Omeprazole was most commonly prescribed PPI. Esmoprazole was second commonest while Rabeprazole was the least prescribed.

DISCUSSION

This study was conducted to review the appropriateness of PPI therapy as there is growing concern about the safety of long term PPI use. Our study population although lives in close proximity of biggest metropolitan of Pakistan, is deprived of basic medical facilities, it is low income population with very scarce education and poor hygienic living condition. Data about PPI use was obtained by auditing the prescription at discharge and reviewing the clinical notes. Further information was obtained by interviewing the patients at the time of discharge.

We found that out of 288 patients admitted 104 were already receiving PPIs. Non of the patients were on H2 receptor antagonist. Prokinetics and antacids were prescribed to 34 and 22 patients respectively. The source of prokinetics prescription was local GPs in 18 cases, in hospital 12 patients, in rest of 4 cases source of prescription was not identified, and all of them were also taking PPIs. Among 22 patients on antacids, treatment initiated by local GPs in 08, by Fatima hospital in 07, and rest of 7 source of prescription was not known.

On discharge 136 out of 288 (47.2%) were on PPIs. A single day audit of PPI prescribing was carried out in 2001 in an Irish secondary care hospital revealed 30.6% patients receiving PPI therapy[4]. Another study in 2003 reported 32% of patients receiving PPI therapy[5]. A valid indication was not apparent in 63% of them. In a London based audit in 1997 only 8% of inpatients were on PPI therapy[6]. This clearly shows a progressive increase in prescribing PPIsduring last 2 decades.

The commonest indication for PPI prescription found in our study was treatment of dyspepsia followed by GORD and healing / prophylaxis of NSAIDs associated ulceration respectively. In our study half of patients on PPI therapy were for unapproved indications. The most common unapproved indication was ulcer prophylaxis in patients on aspirin, clopedogril, steroids or a combination of them. A French study reached at same conclusion that the main non-conform indications of PPIs use were prevention of hemorrhagic risk of anti-platelet agent, anticoagulant, steroids or non-steroid anti-inflammatory therapy without risk factor and continuation of pre-admission PPI prescription without any further assessment of its need.[7]

Another Irish study reported that 32% (87 of 272 patients) were taking PPIs with only 37% having a valid indication[5]. Vliel et al, reported that 40% of patients were taking PPIs for unregistered indications[8].

.**Complications of longterm use of PPIs**

Symptomatic rebound acidity is a common phenomenon after discontinuation of anti-proton pump therapy. Due to acid suppression induced by omeperazole, hypergastrinemia occurs which in turn induces hyperplasia of enterochromaffin like cells. ECL cell hyperplasia causes increased levels of histamine and chromogranin A (CgA) in serum and can be used to evaluate the degree of ECL cells hyperplasia[9]. Rebound hyperacidity could last for 26 weeks after discontinuation of PPIs[10.]

PPI use may increase the risk of community acquired pneumonia (CAP). There is significant dose response relationship in a case control analysis done in Netherlands. Similar observations were made in two case control studies in patients recently commenced on PPIs, although no statistically significant risk was found in long-term users[11,12].

There is much published data to prove positive association between use of PPIs and clostridium difficile associated diarrhea (CDAD) in patients who received antibiotics[13,14]. A prospective case control UK based study showed increased risk of CDAD in hospitalized patients receiving antibiotics and PPI therapy[15]. Statistically significant association of PPI use with CDAD was found in a 5 year analysis[16].

Increased fracture risk and metabolic bone disease has been associated with long term PPI use. The likely cause is effect on bone mineral homeostasis due to effects of PPI on intestinal calcium absorption[17,18,19]. Association of long term PPI use with modestly increased risk of non-spine fracture was found in elderly people with low calcium intake. Although no such association was found with H2RA[20]. Increased risk of hip fractures observed with use of PPIs in a dose and duration dependent manner[21].

Not only calcium homeostasis is disturbed but patients also develop hypomagnesemia and and associated hypokalemia may result in malignant cardiac arrhythmia (Ventricular fibrillation, torsade de pontis, broad complex ventricular tachycardia long QT interval, can also cause neuromuscular abnormalities (muscular cramps, hyperexcitability and convulsions).[22,23,24.]

Clopidogrel is a pro-drug that needs transformation to its active metabolite for its anti-platelet effect. Clopidogrel is activated by CYP2C19, whereas PPIs utilizes the same pathway for metabolism therefore reducing varying degrees the transformation of Clopidogrel to its active metabolite. There has been much interest taken recently in potential drug-drug interaction between clopidogrel and PPIs. Use of clopidogrel with PPI was associated with increased risk of death or rehospitalization from acute coronary syndrome (ACS) compared with use of clopidogrel without PPI[25-26]. Residual platelet aggregation (RPA) was considered as a risk for re-thrombosis in patients undergoing coronary stenting. It was found that peri-procedural co-administration of PPIs significantly decreases the effect of clopidogrel by increasing the RPA[27]. In another retrospective analysis concomitant use of clopidogrel and PPIs in post-percutenous coronary intervention patients was found to be associated with higher risk of major cardiovascular event[28]. United States Food and Drug Administration (FDA) issued an alert stating that PPIs might interfere with the effectiveness of clopidogrel and that clinicians should re-evaluate starting or continuing treatment with PPI in patients taking clopidogrel.

SUMMARY

PPIs are highly effective medicines against acid peptic disease with excellent safety profile but their use in long term is expensive and may be associated with adverse events and possible drug interactions. PPI therapy is not only over prescribed in primary but in secondary setting as well. The extent of their use is evident that 104 (36.1%) out of 288 admissions were already on PPI treatment, and 23.9% of rest of 184 patients received PPI as in patients. Most of iv prescriptions were inappropriate as for as indication is concerned. Many patients were taking high dose PPIs for more than six months to years without a clinical justification. In an area and community like ours patient population, it brings huge economic burden for already economically challenged population. Need not to mention that relatively low cost antisecretory (H2R antagonists), were not prescribed to a single patient. Following prescription guidelines will not only play a role in reducing the cost burden on health care but also decrease the adverse events related to their unjustified use.

REFERENCES

1. Dyspepsia: Management of dyspepsia in adults in primary care, issued August 2004 (guidance.nice.org.uk/cg17.
2. Slattery E, TheyyenthiranR, Cullen G, KennedyF, Ridge C et al. Intravenous proton pump inhibitor use in hospital practice. Eur J Gastroenterol Hepatol. 2007 Jun; 19(6):461-4.
3. Kaplan GG, Bates D, McDonald D, Panaccione R, Romagnuolo J. Inappropriate use of intravenous pantoprazole: extent of the problem and successful solutions. Clin Gastroenterol Hepatol. 2005 Dec; 3(12):1207-14.
4. Mat Saad AZ, Collins N, Lobo MM, O'Connor HJ. Proton pump inhibitors: a survey of prescribing in an Irish general hospital. Int J Clin Pract. 2005 Jan; 59(1):31-4.
5. Sebastian SS, Kernan N, Qasim A, O'Morain CA, Buckley M. Appropriateness of gastric antisecretory therapy in hospital practice. Ir J Med Sci. 2003 Jul-Sep;172(3):115-7.
6. William M, Pounder RE. An audit of proton pump inhibitor usage in a teaching hospital setting. *Gut* 1997; 40: (Suppl 1) A59.
7. Marie I, Moutot A, Tharrasse A, Hellot MF, Robaday S, Hervé F, Lévesque H. Validity of proton pump inhibitors' prescriptions in a department of internal medicine. [Article in French] *Rev Med Interne. 2007 Feb; 28(2):86-93. Epub 2006 Oct 20*
8. van Vliet EP, Otten HJ, Rudolphus A, Knoester PD. Inappropriate prescription of proton pump inhibitors on two pulmonary medicine wards. Eur J Gastroenterol Hepatol. 2008 Jul; 20(7):608-12.
9. Waldum HL, Arnestad JS, Brenna E, Eide I, Syversen U, Sandvik AK. Marked increase in gastric acid secretory capacity after omeprazole treatment. Gut. 1996 Nov; 39(5):649-53.
10. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hyper secretion after long-term inhibition of gastric acid secretion. Aliment Pharmacol Ther. 2005 Jan 15; 21(2):149-54.
11. Gulmez SE, Holm A, Frederiksen H, Jensen TG, et al. Use of proton pump inhibitors and risk of community-acquired pneumonia: a population-based case-control study. Arch intern Med 2007 May 14;167(9):950-5.
12. Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med. 2008 Sep 16; 149(6): 391-8.
13. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA. 2005 Dec 21; 294(23):2989-95.
14. Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. CMAJ. 2004 Jul 6; 171(1):33-8.
15. Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. Aliment Pharmacol Ther. 2006 Aug 15; 24(4):613-9.
16. Jayatilaka S, Shakov R, Eddi R, Bakaj G, Baddoura WJ, DeBari VA. Clostridium difficile infection in an urban medical center: five-year analysis of infection rates among adult admissions and association with the

use of proton pump inhibitors. Ann Clin Lab Sci. 2007 Summer;37(3):241-7.
17. Fournier MR, Targownik LE, Leslie WD. Proton pump inhibitors, osteoporosis and osteoporosis-related fractures. Maturitas. 2009 Sep 20; 64(1): 9-13.
18. Insogna KL. The effect of proton pump-inhibiting drugs on mineral metabolism. Am J Gastroenterol. 2009 Mar; 104(Suppl 2):S2-4.
19. Laine L. Proton pump inhibitors and bone fractures? Am J Gastroenterol. 2009 Mar; 104(Suppl 2): S21-6.
20. Elaine W. Yu, Blackwell T, Ensrud KE, Hillier TA, Lane NE et al. Acid-suppressive medications and risk of bone loss and fracture in older adults. Calcif Tissue Int. 2008 Oct; 83(4): 251-259.
21. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006 Dec 27; 296(24): 2947-53.
22. Ewout J.Hoorn, Joost van der Hoek, RobA. De Man, et al. A case series of proton pump inhibitor-induced Hypomagnesemia, American journal of kidney Diseases, Vol56, No 1 (July),2010:112-116.
23. Giueppe Regolisti, Aderville Cabassi, and Elisabetta Parenti, et al. Severe Hypomagnesemia during Long-term Treatment with a proton pump inhibitor, American journal of kidney Diseases, Vol 56, No 1 (July), 2010:168-174.
24. T. Cundy and A. Dissanayake, Severe hypomagnesemia in long-term users of proton-pump inhibitor, Clinical Endocrinology (2008) 69, 338-341.
25. Khalique SC, Cheng-Lai A. Drug interaction between clopidogrel and proton pump inhibitors. Cardiol Rev. 2009 Jul-Aug; 17(4):198-200.
26. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA. 2009 Mar 4; 301(9):937-44.
27. Zuern CS, Geisler T, Lutilsky N, Winter S, Schwab M, Gawaz M. Effect of co-medication with proton pump inhibitors (PPIs) on post-interventional residual platelet aggregation in patients undergoing coronary stenting treated by dual antiplatelet therapy. Thromb Res. 2010 Feb;125 (2)e51-4.
28. Gupta E, Bansal D, Sotos J, Olden K. Risk of Adverse Clinical Outcomes with Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Percutaneous Coronary Intervention. Dig Dis Sci. 2010 Jul; 55(7): 1964-8

---

[i] **Take home maessage;**

PPIs are safe and relatively without immediate side effects if used for limited period and in proper dose.

When clostridium deficile associated diarrhoea is detected stop PPIs.

In ICU patients keep close check on serum potassium and magnesium levels as their deficiency may result in malignant arrhythmia, including ventricular fibrillation and torsade de pontis.

Drugs for the treatment of Dyspepsia:

Drugs	Mechanism of action
1. Antacids	**neutralise the stomach acids**
2. Alginates	**form protective layer around stomach contents so that harmful acid stays away from stomach wall.**
3. Prokinetics	**enhances gastrointestinal motility by increasing the force and frequency of contractions in the small intestine.**
4. Histamin 2 receptor antagonists	**block the action of histamine on receptor and in parietal cells in stomach and therefore suppress acid secretion.**
5. Proton-pump inhibitors	**Suppress acid secretion by blocking hydrogen/potassium triphosphatase enzyme.**

i