Rationale use of proton pump inhibitors: Observational study of hospital based prescriptions and role of clinical pharmacist

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Abstract: The rationale of acid suppressant therapy with PPIs was assessed to measure the treatments conformity in PGHI under clinical guidelines. The irrational use of PPIs was found to induce side effects in patients and increased budgetary constraint. In a 4 phase study, 2 groups of patients (784 and 2804) were selected; Pre intervention retrospective review of the prescriptions was done in phase I. Insightful awareness in clinicians and patients was created in phase II a and II b respectively. The ongoing prescriptions were intervened in phase III. The post-intervention retrospective audit of prescription was completed in phase IV. The data was recorded for chronic disease patients in the hospital, revealed a marked reduction (85%) in the frequency of PPI's prescriptions (784 to 117), Cost of PPI's /year reduced to 19.3% , from US$: 24522/- to US$: 4718/-. The side effects reported in patients' feedback was also reduced such as hypocalcaemia (59%), hypomagnesaemia (52%), anemia (28%), reflux dyspepsia (82%), C. difficile associated diarrhea (15%), pneumonia (5%), and nephritis in patients with CKD (11%). The intervention induced awareness in Clinicians (85%), in patients (38%), reduction in PPIs prescription (45%), whereas cost of PPI's prescription in group 2 was reduced from US$ 36481/- to US$:10325/- i.e. (28%)

Keywords: PPIs, irrational prescription, clinical Intervention, reduction in side effects and cost of therapy.

INTRODUCTION

Human body has a gastric hydrogen potassium ATPase enzyme (H+/K+ ATPase that functions as the proton pump of the stomach. Proton pump is an integral membrane protein, which is capable of moving protons across a biological membrane (Sakai et al., 2016). These are primarily responsible for the acidification of the stomach contents. H’ ions are generated within the parietal cells from dissociation of water (H2O). These OH- ions rapidly combined with CO2 to form HCO3- ion. This reaction is catalyzed by the enzyme carbonic anhydrase. HCO3 ions are transported out through the basolateral membrane in exchange for Cl- ions and results in minor elevation of blood pH to maintain intracellular pH in the parietal cells. Cl- and K+ ions are transported into the lumen of the canaliculi for secretion of acid. H+ ion which is pumped out of the cell, into the lumen, in exchange for K+ ions through the action of the proton pump. These H+ ions generate osmotic gradient across the membrane by outward diffusion of water and ends in gastric juice which is composed of 155 mM HCl and 15 mM KCl with a small amount of NaCl.

Excessive secretion of gastric acid due to any reason is a major problem usually leading to gastritis, gastric ulcers and peptic acid disease. Hydrochloric acid (HCl) is the component of gastric juice in the stomach and is responsible for the digestion of food. The epithelium of the stomach is intrinsically resistant to the damaging effects of gastric acid. HCL is the secretory product of the parietal cells. The capacity of the stomach to secrete HCl is proportional to the number of parietal cells. Parietal cells bear receptors for three stimulators of acid secretion, Acetylcholine (muscarinic type receptor), Gastrin, Histamine (H2 type receptor), Histamine released constantly from mast cells in the gastric mucosa, thus weak stimulation in acid secretion.

A number of intrinsic substances in the human body are capable of reducing gastric acid secretion. Pharmacologic antagonists of acetylcholine, gastrin and histamine and proton pump can block acid secretion. While glucagon, somatostatin, PGE2 secretin and the gastric inhibitory peptide also have acid suppression effect as the physiologic regulators. Somatostatin inhibits secretion of histamine and gastrin. They show direct inhibitory effect on the parietal cell.

In late 80s H2-receptor antagonists a frequently used acid reducing agent was superseded by proton pump inhibitor (PPI) (Sachs et al., 2006), Their acid suppressing ability was similar to H2 antagonist but more pronounced and long lasting for more than 2 days. This long lasting effect is due to the difference in duration and mode-of-action of PPIs. Majority of the PPIs are benzamidazole derivatives; Their mode of action is based on their irreversible blocking of hydrogen/potassium adenosine triphosphatase (H+/K+ ATPase) enzyme, i.e., the gastric proton pump of the gastric parietal cells, an ideal target to inhibit acid production which in turn reduce gastric acid secretion by more than 90%. PPIs are accumulated in the parietal cell canaliculi and their inhibition is effective on a single copy of enzyme till these enzymes are naturally destroyed and replaced in 2 to 3 days with new copies of the enzyme. Therefore the effect of single dose of PPIs is effective

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upto 2 to 3 days because of the irreversible nature of proton pump inhibition but its effect on the overall human digestive system is reversible after 3 days. With PPIs the reduction of acid, lessen the irritation on the wall of the stomach in turns reduces ulceration and reduces pain due to indigestion and heartburn. It further helps in healing of the duodenal ulcers. Pharmacokinetics effect has no significant impact on efficacy. Rate of absorption of PPIs is decreased and delayed by concomitant food intake. In normal subject a reasonable acidic media in stomach does not render various kinds of bacteria to grow because acidic pH eliminates pathogenic organism from GIT but long term use of PPIs causes prolonged acid suppression and may leads to increase in gastrin secretion (hyper gastrinemia) that allows production of various bacterial and carcinogenic substances. It is therefore suggested that plasma gastrin levels should be monitored in patients on long term PPIs therapy. Community acquired pneumonia is reported in patients on long term therapy of PPIs, specially in hospitalized patients of pulmonary diseases (Ryder et al., 1994, Niklasson et al., 2003, Laheij et al., 2003, 2004 and 2010, Cooper et al. and Simpson et al., 2006, Kahrilas et al., 2008. In hospitalized patients at higher risk of pneumonia, it is suggested that PPIs should be prescribed only when necessary in lowest effective dose Laheij et al., 2003, JAMA 2004, JBMH 2010, Eom et al., 2011). PPIs are well tolerated for short term use. Their short- term adverse effects are rarely observed and not fatal (can be flatulence, constipation, rash, itch, anxiety and depression). Long term PPIs treatment can induce and enhance various pathological factors (hypocalcemia, hypomagnesia, iron and vitamin D3 and B12 deficiency due to raised pH in case of end stage renal disease, It was reported in a study that patients older than 50, taking PPIs for longer than 1 year in high doses were 2.6 times more likely to break a hip. If taking PPIs in smaller doses for more than 2 years were 1.2 to 1.6 times more likely to break a hip. The risk of a fracture is directly proportional with the length of time and strength of PPIs dose intake (Eom et al., 2011, Sturniolo 2011). The FDA review of studies on the evaluation of risk fracture related with long term use of PPIs. It was reported that the risk of fractures of wrist, spine and hip, increased with PPIs use in individuals aged 50 or older due to reduction in gastric acid by PPIs as at high pH the calcium dissolved in the stomach is less likely to be absorbed in the bone, and thus interferes the phenomena of breakdown and rebuilding of bone by interfering with the acid production of osteoclasts (Yang et al., 2006, Seppa et al., 2007, Targownik et al., 2008, DeVries et al., 2010). It is an intrinsic action of gastric acid (HCl) in the stomach, to release B12 from food particles. So hypochlorhydria due to long term use of PPI’s also decreases vitamin B12 absorption which may leads to vitamin B12 deficiency (Jensen et al., 2010). This deficiency may also increase bone fragility by raising homo-cysteine. Sufficient hydrochloric acid is required for the digestion of proteins, for the absorption of nutrients particularly vitamin B12, calcium and iron. Long term PPIs treatment can induce hypocalcemia, hypomagnesia, iron and B12 deficiency due to raised pH in stomach. This condition is also observed in end stage renal disease (Adelaïde et al., 2006 and Heidelbaugh et al., 2013). In one of the study, it was reported that one week after the discontinuation of treatment of pantoprazole, a dyspepsia was observed in 44% recipients this was “rebound hyperacidity” Referring this report, FDA has advised that PPIs should not be used in dyspepsia or heart burn for more than three 14-days treatment courses in one year (Pillans et al., 2005, Bisanth et al., 2007, Wang et al., 2007, Niklasson et al., 2009). In 2010 and 2011 the U.S. (FDA) had released a notice for public and healthcare professionals that the prescription of PPIs for longer than one year leads to reduction in serum level of prolactin and magnesium i.e. hypoprolactinemia, hypomagnesemia (Jabbar et al., 2010).

Clinically licensed indications

Most of the clinical guidelines (McManus et al 1998 and Martin et al., 1998, Radford et al., 2000, Baulkham et al., 2004), expressed the following labeled indications of PPI’s use: The long term treatment of duodenal and gastric ulcers, Zollinger-Ellison syndrome, Barrettes disease (Rossi et al., 2006). It should be treated with a healing dose of a PPI until the symptoms have been controlled. PPIs heal ulceration but do not reverse epithelial changes of Barrett’s esophagus (Cooper and Chapman et al., 2006) in severe reflux esophagitis, erosive esophagitis (GERD), in high risk GI bleed during long term NSAIDs and glucocorticosteroids therapy as a prophylactic agent to prevent medicine induced ulcer, in high risk lesion at endoscopy, and in case of infectious peptic ulcer disease induced by H. pylori (Yuan et al., 2013) for pre-anesthetic therapy to prevent acid aspiration pneumonia during operation. PPIs are also co-prescribed to support antibiotic therapy to reduce stomach ulcer by acid suppression it causes increase in stomach pH for it’s more pronounced and long-lasting reduction in gastric acid production:

• PPIs should be prescribed only in the licensed indications, appropriate to the clinical need of patients in doses that meet their own individual requirements for an adequate period of time.

• H pylori infected ulcer should be rule out through diseased specific clinical investigations, if H. pylori infectious ulcer is positive, treated for 7 to 14 days concomitantly with antibiotic regimen and PPIs for complete eradication of infection.

• For an ulcer or erosive esophagitis it is continued for 4 to 8 weeks. In case of documented duodenal or gastric ulcers, or erosive esophagitis, PPI is appropriate to use for symptom control until ulcers heal, at least for 6 to 8 weeks.
For long term treatment of gastro esophageal reflux disease (NICE guidelines 2000). Possibly the lowest effective dose of proton pump inhibitors could be prescribed to achieve the desired therapeutic effect.

Treatment with low dose PIs as a maintenance dose prevents recurrent GERD symptoms in 80% patients

In case of uninvestigated dyspepsia, PPIs may be given in full dose for one month to assess response. Patient with mild symptoms of dyspepsia or non-ulcer dyspepsia (NUD), does not generally benefit from a PPIs treatment. He may be prescribed a short, low dose course (1-2 week). Regularly review to assess the

Patient’s response, then step down to less potent medication where possible

Uncomplicated dyspepsia and non-specific abdominal symptom can be very well treated with other less expensive acid reducing agents.

MATERIALS AND METHODS

Patients and method

Hospital setting
The study was carried out a tertiary care hospital with 300 beds, providing health care facilities to outdoor and indoor patients. Study population was comprised of the employees of an organization and the private patients.

Permission of Ethical Committee
Permission was obtained from ethical committee of the hospital before starting the observational study and intervention. The committee was comprised of Consultant Gastroenterologist, Consultant Medical Specialist, Consultant Orthopedic, Consultant Nephrologist, Consultant Rheumatologist, Director of the Hospital.

Patients
The patients in the study did not fall in the criteria for clinically safe indications for prescribing PPI’s except the patients with musculoskeletal disorders and CKD who were prescribed PPIs as prophylaxis to prevent NSAIDs and steroids induced gastric ulcer. The study patients were divided in 2 groups.

Study population
Group 1: Adults patients (784) with different chronic diseases on prolong treatment, visited outdoor pharmacy for collecting medicines on monthly basis. Their prescriptions for the period of 2010-2011, were assessed in Dec, 2011, for the use of PPIs they were taking continuously over a period of 2 years.

Group 2: These patients were included during intervention period comprised of adult patients admitted in ICU, wards of Medical, Psychiatry, Orthopedic, Gynecology and Surgical and emergency units. The medicine charts and patients files during hospitalization were reviewed with particular interest in the diagnosis on admission, pharmacological treatment employed, including acid suppressive medicines, their doses, the time of intake and the reason for the prescription. The intervention is done if applicable on daily basis before unit dose dispensing in indoor pharmacy for every indoor patient.

Study was performed in 4 phases: Phase-I. Retrospective study was performed on 784 ambulatory patients with different chronic diseases. The pre-intervention analysis of the prescriptions of chronic disease patients was carried out in December 2011, for a period of 2 years (Jan, 2010 to Dec, 2011).

Phase II: Step-a. Pharmacist collaborated with medical ethical committee (relevant consultants, medical specialist, and gastroenterologist). The patient's prescriptions for PPIs were discussed to evaluate the reason behind prescription of PPIs. Consultants of clinical specialties including medical OPD, rheumatology, orthopedic were interviewed on the trend prescribing practice and share the recommendations on therapeutic guidelines for the approved indications to prescribe PPIs.

Phase II: Step-b. Pharmacist counseled and educated ambulatory patients: Record for each patient included age, disease history, medical history, reason for PPIs prescription along with the chronic disease's prescription, duration of PPI's prescription, in case of hospitalized patients, and reason for admission, were compiled. Ambulatory patients were asked short series of questions during visit to outdoor pharmacy to obtain their prescribed medicines. The pattern of questions asked were about their disease history, medication history, current symptoms, life style, eating habits and choice of daily food intake. The patients who need intervention in their prescriptions were counseled and educated to taper off PPIs slowly to prevent occurrence of rebound hyperacidity and dyspepsia. They were convinced to give up the continuous use of PPs due to which they would be vulnerable to other chronic diseases and to avoid its side effects and interaction with certain other prescription medicines they were using concomitantly.

Phase III: Intervention was commenced gradually since Jan, 2012 and it was kept on continued by the end of 2014. In the first month of intervention the patients who were taking PPIs as BID dose their dose was reduced from 60 to 30 tablets/month as an OD dose. Next month their dose was further reduced to 15 tablets/month, one tablet every alternate day Ispaghula husk gel (Ispaghula husk 1 table spoon + 1 cup of water give 10 minutes to form gel) 1 cup/day was added to their prescription. In the coming month the dose was further reduced to 7 tablets/month i.e., one tablet on every 3rd day and the Ispaghula husk gel, twice a day once before breakfast and then at bed time was added to their prescription. The consultants
also cooperated. In 5% patients PPIs were supplemented with H2 antagonist and gastroprokinetic agents to suppress night time symptoms of heart burn and gastro paresis respectively. The patients were further advised to take high fiber diet and increase fluid intake.

Intervention was also implemented in two thousand eight hundred and four (2804) hospitalized patients of Group-II. This group also include elderly patients admitted in Intensive Care Unit (ICU), medical ward for the treatment of acute symptoms of chronic diseases due to age related diseases like asthma, COPD, or patients admitted in wards for surgical procedures under general surgery, urology, Ear Nose Throat (ENT), gynae and orthopedics clinics. These patients were already taking PPIs before admission, because of discomfort of dyspepsia, acidity or gastroparesis associated with diabetes mellitus, their sedentary life style, inappropriate eating habits, limited movements because of old age, osteoporosis, osteoarthritis R.A, etc.

As per limitations of the ethical medical committee, no drastic intervention was carried out in clinical management based on PPI’s prescription in the hospitalized patients. The mutual consent and recommendations of consultants and senior Gastroenterologist allowed only that the bid oral dosing of PPIs could be reduced to OD dose if seen in medicine chart of these patients.

Phase IV: Post intervention audit of the prescription was carried out in the middle of 2014. Intervention and audit was continued for further six months. Data collection was performed to evaluate trend and pattern in prescriptions after intervention.

RESULTS

The retrospective analysis of the prescription of PPIs in patients of group I, and in group II in pre-intervention phase I and in post intervention phase IV was recorded in table 1-4 for group I and table 5-7 for group II. The results obtained are recorded first for group I and then for group II. After thorough review of last 2 years prescriptions of Group I, record was compiled in table 1 revealing the reason of prescription, pattern and history of prescription, strength, dose of PPI's, and number of patients obtaining these medicine every month as prolong medical treatment. The pre-intervention retrospective cost analysis of 784 prescriptions was also carried out and recorded in table 2, showing the cost of PPIs consumed before intervention. PKR 24,52183/- (US$: 24522/-).

In consequence of appropriate intervention over 3 years, the post-intervention retrospective analysis for a period on one year (Jan-Dec, 2014) carried out at the end of the study and was recorded in table 3 and fig 2., (PKR 4,71766/- (US$: 4718).
**Table 1:** Group 1 Prescriptions of chronic disease patients on prolong treatment (2010-2011), do not have potential GIT disorders

<table>
<thead>
<tr>
<th>Reason of Prescriptions</th>
<th>Pattern of Prescriptions in Patients</th>
<th>Reason of PPIs use</th>
<th>PPI's Dose/m/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I A=500 HTN, CVD, CAD + DM, D M alone Dyslipidemia</td>
<td>(ASA±Clopidogrel, Amlodipine/ - Blockers, Statins, (Acetaminophen+Thioridazine:500/3mg),± Nimsulide/Celecoxibs/ Diclofenac Potassium, Esso / Omeprazole 20mg OD)+ (Inj. Human Insulin R, Insulin Glargine/Detemir ± Glimpiride, Metformin, Wildaglyptin or Sitaglyptins , Pregabalin)</td>
<td>Dyspepsia, heart burn, gastroperesis</td>
<td>20mg OD 30/m, 360/yr</td>
</tr>
</tbody>
</table>

**Table 2:** Pre-intervention cost analysis of prescriptions of chronic disease patients under prolong treatment of PPIs (2010-2011)

<table>
<thead>
<tr>
<th>Reason of Prescriptions/ PPI's</th>
<th>PPI's Strength</th>
<th>Cost PKR</th>
<th>Dose of PPIs/yr/ Patient</th>
<th>No of Pats</th>
<th>Cost of PPI's consumed /yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - CAD/HTN/DM/ Dyslipidemia</td>
<td>Omeprazole 40mg</td>
<td>6.43</td>
<td>360</td>
<td>500</td>
<td>1157400/-</td>
</tr>
<tr>
<td>B- ESRD, CKD, Ren. Transplant, RA, SLE</td>
<td>Esso 40mg</td>
<td>14.14</td>
<td>720</td>
<td>74</td>
<td>7,53,379/-</td>
</tr>
<tr>
<td>C- Hep C/ Hep B</td>
<td>Omeprazole 40mg</td>
<td>6.43</td>
<td>360</td>
<td>150</td>
<td>347220/-</td>
</tr>
<tr>
<td>D- Asthma/COPD, Neuro./Psych./, Others</td>
<td>Esso 20mg</td>
<td>8.99</td>
<td>360</td>
<td>60</td>
<td>1,94184/-</td>
</tr>
</tbody>
</table>

Net Expenditure of PPIs/year in a hospital

784 PKR 24,52183/- US$ 24522/-

**Table 3:** Post-intervention cost analysis of prescriptions in chronic disease patients on prolong treatment of PPIs (2014)

<table>
<thead>
<tr>
<th>Reason of Prescriptions/ PPI's Strength</th>
<th>PPI's Strength</th>
<th>Cost PKR</th>
<th>Dose of PPIs/yr/ Patient</th>
<th>No of Pats</th>
<th>Cost of PPI's consumed /yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - CAD/HTN/DM/ Dyslipidemia</td>
<td>Esso 20mg</td>
<td>8.99</td>
<td>360</td>
<td>25</td>
<td>80910/-</td>
</tr>
<tr>
<td>B- ESRD, CKD, Ren. Transplant, RA, SLE</td>
<td>Esso 40mg</td>
<td>14.14</td>
<td>720</td>
<td>69</td>
<td>351238/-</td>
</tr>
<tr>
<td>C- Hep C/ Hep B</td>
<td>Omeprazole 40mg</td>
<td>6.43</td>
<td>360</td>
<td>12</td>
<td>27778/-</td>
</tr>
<tr>
<td>D- Asthma/COPD, Neuro./Psych./, Others</td>
<td>Omeprazole 20mg</td>
<td>2.99</td>
<td>360</td>
<td>11</td>
<td>11840/-</td>
</tr>
</tbody>
</table>

Total Expenditure of PPIs /year in hospital after Intervention

101 PKR 4,71766/- US$ 4718/-

Cost of PPIs consumed/ yr of each Strength= formula for calculation: Cost of PPI’s (strength) consumed /yr = unit rate x No of Patients x dose x days x m. eg. Omeprazole 20mg /yr= 2.99 x 1 x 30 x12 x x 500 = 5,38,200

**Table 4:** Comparison of pre and post intervention cost of PPI’s prescriptions retrospective review in ambulatory patients (Chronic Diseases)

<table>
<thead>
<tr>
<th>Reason of Prescriptions</th>
<th>Pre-interv. Cost of &quot; /yr in 784 patient</th>
<th>Post Intv. Cost Reduc. in 101 patients</th>
<th>% age of &quot; reduced in 3 yrs</th>
<th>Post Intv. No. &quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-CAD/HTN/DM/ Dyslipidemia</td>
<td>5,38,200/-</td>
<td>12917/-</td>
<td>&gt;95 %</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>B-ESRD, ckd, renal transplant, ra, sle</td>
<td>7,53,379/-</td>
<td>351238/-</td>
<td>&gt;7%</td>
<td>69 ± 5</td>
</tr>
<tr>
<td>C- Hep C/ Hep B</td>
<td>4,85,460/-</td>
<td>32364/-</td>
<td>&gt;93%</td>
<td>10 ±5</td>
</tr>
<tr>
<td>D- Asthma/COPD, Neuro/ Psychiatry &amp; Others</td>
<td>2,31,480/-</td>
<td>23148/-</td>
<td>&gt;83%</td>
<td></td>
</tr>
<tr>
<td>Net Expenditure in PKR</td>
<td>Pk.R=20,08519/-</td>
<td>4,19666/-</td>
<td>~ 13%</td>
<td></td>
</tr>
<tr>
<td>Net Expenditure in US$</td>
<td>20,085/-</td>
<td>4,196</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rationale use of proton pump inhibitors

Table 5: Reason and Pattern of PPIs in Prescription Chart of Hospitalized Patients (Group 2)

<table>
<thead>
<tr>
<th>Reasons of &quot;&quot;, # of patients</th>
<th>Pattern of Prescription Charts</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-2 A: 830 patients Elderly Patient in ICU</td>
<td>(ASA ± Clopidogre), Amlodipine, Statins, Acetaminophen+Thioridazine (500/3mg), +Nimisulide, +(Inj. Human Insulin R, Insulin Glargine /Deteremir ± Glimpiride, Metformin, Wilda/Sita-glyptins, Pregabalin, Injection Tramadol 100mg, etc. Inf. Omeprazole 40mg bid</td>
</tr>
<tr>
<td>G-2B: 144 Patients, Acute musculoskeletal pains: L. back, spondylitis, Frozen shoulder, others</td>
<td>Inf. Ketorolac 30mg tds, Tab Tramadol 100mg, bid, tab(Cyclobenzabrine /Tizinadine+ Acetaminophen) tds, Tab Aclofenac 100m either Meloxicam 15mg bid tab Essoomeprazole 40mg, Bid)</td>
</tr>
<tr>
<td>G-2C: 1140 patients, Surgery, Orthopedic, ENT, Urology, Gynecology, &amp; Others</td>
<td>Leproscopy for gall stone (average no of patient 300/yr: 1. Pre-Op and 2post-Op. for 2nd day Bid infusions of Omeprazole then switched to oral Omeprazole OD +/Aggressive NSAIDS Th.: Inf. Ketorolac 30mg tds, Inj. Tramadol 100mg tds, Tab Thioridazine+ Acetaminophen 3/ 500mg tds), Tab Aclofenac /Meloxicam 100/15 mg bid,</td>
</tr>
<tr>
<td>G-2D: 690 patients, Medical ward, Acute cases of Infectious Diseases Neuro/Psychiatric disorders, CVD, Respiratory disorders.</td>
<td>Asthma: Inhalation of B2 agonist, oral/ injectable steroids + inhalation steroids, ± oral theophylline/ its derivatives, leukotriene inhibitors, Anti-epileptic, -psychotics, dipressant, anxieolytics Or Antihyperensive/vasodilators/lipid lowering agents, Omeprazole switched to Essoomeprazole with antiplatelet drugs.</td>
</tr>
</tbody>
</table>

Table 6: Pre-intervention expected cost of prescriptions of PPIs demanded in hospitalized patients admitted for acute illness. during 5 days stay.

<table>
<thead>
<tr>
<th>Reasons For &quot;&quot;, # of patients</th>
<th>No of PPIs Oral, I/V Preps</th>
<th>Cost PKR</th>
<th>5 days stay Total Cost of PPIs Consumed in indoor patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-2 A (830 x 2 x 5d. Elderly serious Patient in ICU</td>
<td>Inf. 8300</td>
<td>250</td>
<td>20,75000/-</td>
</tr>
<tr>
<td>G-2 B. 144 x 2 x 5d. Patients Acute L. back pain, spondylitis, frozen shoulder, (MSK pain)</td>
<td>Tb. Esso 40mg :1440</td>
<td>14.14</td>
<td>20361/-</td>
</tr>
<tr>
<td>G-2 C. Laprotomy: Inf:(300x3x1d.),+ (300x2x2d) Oral:m300 x2 x 2d 840: Orthopedic, Urology, ENT, Gynecology, Other</td>
<td>Omp Inf 900+1200 Cap Omp 40mg 1200 Tb. Esso 40mx: 8400</td>
<td>250</td>
<td>5,25000/-</td>
</tr>
<tr>
<td>G-2 D. (690x2x5d.) Medical ward, Acute Infectious Diseases Psychiatric disorders/ Acute CVD, Acute Asthma/ Respiratory disorders etc.</td>
<td>Cap Omp: 6900</td>
<td>6.43</td>
<td>44367</td>
</tr>
<tr>
<td>Total Expenditure of PPIs /year in hospital before Intervention</td>
<td>PKR 36,48106/- US$ 36481/-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A comparison in pre and post intervention prescription and reduction in the cost of therapy in Group I patients is very obvious in table 4 and fig 3 (PKR: 19,80,417/-, US$:19804).

Clinical awareness created in clinicians of the hospital was 85%, Patient education on life style improvement was achieved 38% patients awareness that any medicine if taken for any short term symptomatic treatment, should not be used after these symptoms were resolved was also achieved in 38% patients long term use of any medicines and avoid to unnecessary of medicine after asymptomatic.

On the other hand 45% patients were prevented to continue PPIs by replacing with less expensive acid suppressive agents H2 antagonist, (25%), by stopping treatment for acid suppression and managed the patients with non pharmacological measures (life style and diet. in 22% of patients.

In hospitalized patients (group-II), the sub groups of category of patients are listed in table. 5 (Gp II-A, B, C and D) with reason and pattern of prescription.

The pre-intervention audit of the prescription chart of each patient of GP II was assessed for expected cost of prescription. The record of each assessment is recorded in table 6. The post intervention record of PPI’s consumption is shown in table 7 and illustrated graphically in fig. 4. The result of intervention showed marked reduction in cost of therapy / (from PKR 36,48106/- (US$: 36481/-) to PKR 10, 32512 (US$:10325) per year. The feedback on therapeutic outcome of acid suppression and GIT symptoms control post intervention was also satisfactory.
DISCUSSION

PPIs have become one of the most commonly prescribed drug being the most potent and effective in treating acid related disorders of GIT. Its long lasting acid suppression is due its prolonged duration of action (up to 3 days) which is the leading cause for worldwide use of PPIs. Number of studies on PPIs long term use revealed the appearance of some side effects which effect patient’s health adversely by preventing absorption of useful trace elements and vitamin, by providing higher GIT pH which promote the growth of bacterial infection. The FDA and WHO, have approved clinical guidelines under which safe use of PPIs do not harm the patients.

The current study was undertaken to evaluate the trend of PPIs prescription in our tertiary care hospital in Group I (chronic disease patients on prolong medical treatment) and Group II (patients hospitalized for 5 days for the treatment of acute illness). The retrospective analysis (phase I) undertaken for last 2 year’s prescriptions in patients of group I. In table 1 the reason for prescription, the pattern of prescription and dose of PPIs given to these patients in combination with their chronic disease related medicines and the no patients under specific disease (sub groups) are recorded. Patients' disease and medical history revealed that the reason to continue PPIs in most of the patients had no definitive GIT related indications. The cost of therapy was calculated in these patients showing the huge expenses (table 2 and fig. 1) as cost of PPI’s treatment only for mild dyspepsia, heart burn and discomfort due to constipation. The PPIs were continued by physicians only to manage these symptoms for the satisfaction of patients. In some patients PPIs were prescribed for the symptoms which had already been resolved. These prescriptions were discussed with consultants, gastroenterologist and with permission of Institutional Ethics Committee (IEC), the study was proceeded further.

In Phase II, step a. was the judicious awareness which was created in clinicians by the clinical pharmacist on rational prescribing practices and the hospital policy was established under clinical guidelines, convinced practitioners to prescribe PPIs only where true indications are present.
Rationale use of proton pump inhibitors

will be diagnosed for the use of this group of medicines. In Phase II, step b was the initiation of awareness in patients (group I) by counseling and educating them to improve their eating habits, lifestyle, selection of food items, water intake to resolve the problem of dyspepsia, heartburn and constipation usually occur to bad lifestyle and eating habits. They were also educated that long term use of PPIs could be the cause of deficiency of vitamins and trace elements like B12, calcium, iron, magnesium etc and the occurrence of certain infectious diseases.

In phase III, The prescriptions of 784 patients of Group I were selected and the patients who were continued on prolonged medical treatment of their different chronic diseases excluding potential GIT disorders. Patients were followed by counseling, education, intervention gradually and regular feedback was retrieved on each monthly visit for the next 3 years. The gradual intervention was kept continued by the pharmacist and gastroenterologist and PPIs were kept continued in this group (I) only in patients if appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and to the hospital and organization.

The post intervention audit of prescriptions was done for the period of Jan to Dec, 2014 in phase IV, (table 3 and fig, 2 and 3), to calculate the post intervention cost reduction of PPIs therapy in groups I. It was found that out of 784 (group I) patients 20±5% (117) were remained continued on PPI's prescriptions. In sub group IIA (CAD, HTN, metabolic disorders), Only 5% of patients need to continue PPIs, while 95% patients were intervened. PPIs were either replaced with low dose H2 antagonist (15%) or replaced with Ispaghula husk gel, twice a day (35%), the remaining (40%) patients of age group of 35-55 years were managed without acid suppressive agents, with high fiber diet (vegetables, fruits, and bran), increased water intake, regular exercise to improve their GIT motility. In 5% patients in this sub group, need to continue PPIs. In 74 patients of Group I-B (ESRD, CKD, renal transplant, SLE, R.A the frequency of PPI's prescription could be reduced only from 74 to 69 patients [5±2 (7%)], very little intervention could be done because they were given PPIs prophylactically against anti-inflammatory and immunosuppressive medicines as long term treatment of chronic illness. In this sub group I-A and I-B, esomeprazole was kept continued but twice a day (BID) PPI's dose was reduced to once a day OD dose. Esomeprazole does not antagonize antiplatelet drugs (clopidogrel). On the other hand in sub I in case of patients (74) sub group IB, age ranges from 25-70 years, reason of prescription, as follows: R.A, CKD, ESRD, SLE, or Renal transplant, very little intervention could be done because these patients were on long term treatment of steroid, NSAIDs and immunosuppressive drugs. PPIs were prescribed to these patients for prophylaxis against potent gastric irritant drugs medicines (prednisolone, NSAIDs, Methotrexate, Leflunamide or Cyclosporine, Certican etc). Reduction in PPIs prescription in this group was achieved only in asymptomatic patients of age below 30 years (6.75%) while most of the patients in this group were not considered for intervention to maintain their quality of life.

Group 1C patients of HCV and HBV (age 21 to 56 yrs) The intervention reduced the patient on PPIs from 150 to 12 prescription (83%) by the end of 2014. In this group the patient are followed for 3 years because for the 1st year of treatment they were receiving treatment with conventional interferon for 6 months to 1 year, On their follow up visits few of them diagnosed with recurrence and other were diagnoses with relapse of Hep C cases (during 2010 to 2011). These patients were switched to treatment with pegylated interferon. The adverse effect profile in these was reduced in these patients when responding with peg interferon treatment. Hep B. patients were also maintained on oral antiviral treatment. The 150 patients (Hepatitis B and Hepatitis C) fall in group I-C. During 2010 and 2011 they were treated with 72 injections of conventional interferon for 24 weeks to achieve sustained viral response. Later in follow up visits they developed recurrence and or relapse. These patients were then treated for 48 to 72 weeks with Pegylated interferon to obtain very low HCV qualitative report by real time PCR. The prescriptions of this group of patients could be followed due to their long term follow up visits with regard to the complications of disease; recurrence, relapse of hepatitis viral infection. After discussion with gastroenterologist it was decided by the consultant that in future PPIs will be prescribed only in elderly patients with Hepatitis B and C, who had severe discomfort due to dyspepsia or GERD.

Later the same population of group 1C, visited OPD of PGHI, because by real time PCR their reports again showed the qualitative HCV load varies from positive to highly positive (20,000-800,000 to >800,000). These patients were planned to treat further with newly induced oral antiviral agent sofosbuvir.

The number of PPI's prescription in this group of patients coming to outdoor pharmacy for follow up treatment of HCV and HBV, was further reduced by the end of 2014 to 12 prescriptions i.e., reduction from 100 to 8%.

Group 1D (Asthma, COPD, neurological, psychiatric disorders and other chronic diseases), In this group the number of patients on PPI's prescription was reduced from 60 to 11 patients (83%). Only in 9 to 10 elderly patients with age beyond 70 years, were kept continued due to uncontrolled symptoms of GERD and improve their quality of life. The post intervention cost analysis
Patients of asthma, psychiatric and neurological disorders Gp I D (11%). They were kept continued with PPIs therapy because of old age and lack of gastroparesis. The remaining patients of these 2 subgroups were managed education, life style improvement and non pharmacological measures.

The overall awareness and education achieved by the pharmacist in patients was 35%. The efforts done by clinician to step down PPIs therapy or to switch to other acid suppressants was achieved in 42% patient i.e., reduction in frequency of PPIs prescription. The cost analysis revealed (table 3, fig. 3), overall cost reduction in the consumption of PPIs in chronic diseases patients. Was more than 15,000 US$ (15 lacs PKR) per year?

In Group II the hospitalized patients, the categories selected were divided in further sub groups, relevant to the type of acute illness to be treated during 5 days stay in a hospital. The pre-intervention audit of the prescription chart of indoor patients of Gp II was discussed with ethical committee of hospital. Every chart was assessed for expected cost of prescription. The record of each assessment is registered in table 6 PKR 36,48106/- (US$: 36481/-) limited intervention could be carried out as per decision of ethical committee. Therefore intervention used in this study had comparatively lesser effect on the proportion of patients taking a PPI at the time of hospital admission, but the reduction in the dose of PPIs significantly reduced the cost of indoor prescriptions of PPIs.

For elderly patients in ICU not able to take oral therapy, Infusion Omeprazole is given at day time and injection ranitidine given at bed time 291 patient who can take oral medicines are treated with oral dosage form of PPIs day time and oral H2 antagonist at bed time The intervention in Sub group II A, elderly patients (830) in ICU who could not treated with oral medication (539) Slow Infusion of Omeprazole was given for day time acid suppression while nocturnal symptoms were managed with Injection ranitidine (H2 antagonist. 291 patients able of oral intake and patients of II-D with CAD were maintained with essomeprazole 40 mg in the morning and oral ranitidine 300mg at bed time. Patients in group II-Band group II C, Essomeprazole was replaced with Omeprazole due to lesser unit cost. Patients of group IIC admitted for laprotnomy, the number of infusion of omeprazole were reduced, on day 1 2 infusion, on day 2, one infusion of PPIs and bed time infusions was replaced with injection ranitidine. For the next 3 days these patients were switched to oral dosage form of omeprazole. PPIf The result of intervention showed marked reduction cost of therapy / (from PKR 36,48106/- (US$: 36481/-) to PKR 10, 32512 (US$:10325) per year and post intervention record is registered in table 6. The same is illustrated graphically in fig. In group II Essomeprazole 40mg was given orally before break fast and oral ranitidine 300 at bed in 291 elderly patients in ICU, in group II A and in patients with cardiovascular disorders (CVD) of group II D, In. The feedback on therapeutic outcome of acid suppression and GIT symptoms control post intervention was also satisfactory in group II patients. Patients with other surgical procedures were maintained on oral PPIs (omeprazole). The oral twice a day BID dose of PPIs was also reduced to once a day OD dose. Essomeprazole was replaced with Omeprazole due to lesser unit price. The post intervention audit showed 50% reduction in prescriptions and thus cost of prescription was also reduced to 50%, i.e., from PKR 36,48106/- (US$:36481 to PKR 10, 32512 (US$:10325) For elderly patients in ICU not able to take oral therapy, Infusion Omeprazole is given at day time and injection ranitidine given at bed time 291 patient who can take oral medicines are treated with oral dosage form of PPIs day time and oral H2 antagonist at bed time.

On the basis of current study there are few recommendation which helps clinical practitioners to promote the rational use of PPIs:

1. The prescription of PPI's should be selected only for a valid indication with a consideration of the risk-benefit ratio of the therapy prescribed. The discontinuation of any treatment is being considered even at a slight risk
2. The short-term use of PPIs have a high margin of safety, where as their long term use is associated with potential risk factors that have also been reported extensively and observed in patients understudy.
3. If the PPI is needed for long term therapy e.g. for the relief of symptoms of dyspepsia when co-prescribed with NSAIDs, steroids, immunosuppressive medicines or non erosive gastro esophageal reflux disease, elderly patients, the dose of PPI should be prescribed as minimum effective dose to maintain symptom control.
4. In many GIT related disorders like uncomplicated dyspepsia, non-specific abdominal symptoms, without acid related features can be very well treated with other less expensive acid reducing agents.
5. Patients with chronic musculoskeletal disorders (OA, R.A, SLE etc) taking long term non-steroidal anti-inflammatory drugs (NSAID), steroids or aspirin, PPIs should be co prescribed to prevent NSAIDs, and steroid induced ulcers. When pain symptoms are controlled, NSAIDs and then PPIs can be tapered off.
6. Patients with musculoskeletal disorders (R.A, O.A, kept continued on prolong medical treatment of

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DMRAD, Steroid, BRMD and NSAIDs, The NSAID’s, and steroid should be tapered off once their disease is controlled with the treatment of DMARD/Biological Response modifier. Consequently the PPIs dose should also be tapered off or patient can either switch to less aggressive acid suppression agents (antacids, $H_2$ antagonist.

7. Patients with ESRD, CKD, Renal Transplant treated with immunosuppressive agents, can be switched to $H_2$ antagonist because these patients are already severely experiencing hypocalcemia, deficiency of Iron, vitamin B$_{12}$ and D$_3$, due to their malfunctioned kidneys. They have to take high dose calcium, vitamin D, Iron and B complex preparations. PPIs strongly interact with these supplements and prevent their absorption in the body by raising the pH of gastrointestinal tract over 24 hours and thus aggravate these deficiencies further.

8. It is suggested to maintain these patients for dyspepsia and heart burn with $H_2$ antagonist, Ispaghula husk or antacids. It is further recommended to administer their therapeutic medicines (CKD ESRD etc. in these patients at least 1 hour before giving the dose of trace elements, iron, calcium supplements and vitamins, in order to get therapeutic concentration of these medicines in the blood for maximum therapeutic outcome.

9. It is further recommended to clinicians that do not advise more than 3, fourteen days treatment/year with PPI’s in one patient for the symptoms of dyspepsia and heart burn. Advise such patients to improve their life style and eating habits to treat these minor symptoms.

The elderly patients are more likely to get various infections due to reduced immunity, chronic deficiency of various physiological parameters. Thus the increased use of PPIs in elderly should also be evaluated and they should be prescribed minimum effective dose.

10. In patients who have licensed indication for the use of PPIs (Gastric/Duodenal Ulcer, GERD, Barrett’s and Zolinger Eddison’s Syndrome), it is also recommended that they should also try life style modification like smoking cessation, cut down in dietary fat intake, taking more fluid intake, moderate physical activity, selection of healthy food, always taking evening meal 3 hrs before bed time, and weight loss in over weight patients as an adjuvant to the treatment with these expensive medicines.

11. Plasma gastrin levels should be monitored in patients on long term PPIs therapy.

**CONCLUSION**

Rationalize the use of PPIs in population of patients visiting this tertiary care hospital. Pharmacist have to put efforts to play a role of clinical pharmacist in order to educate patients and to share clinical guidelines and drug related information with ethical committee, and consultant of all clinical specialties The current study revealed that patients getting medications for other chronic diseases were receiving PPIs regularly as a prolong treatment for poorly defined symptoms where PPIs have not been shown to be useful like

- Non-specific abdominal symptoms without acid related features, 
- co-prescribed with aspirin, NSAIDs or corticosteroids in asymptomatic patients 
- Commonly receiving a long term repeat prescription for a previous problem which had been since resolved.

In this way the acid-suppressive agents are over used in ambulatory and hospitalized patients with different chronic diseases, minor and acute illness. Most inappropriate prescriptions were prescribed to patients only with mild dyspepsia which was found to be due to sedentary life style and bad eating habits. The prescribing trends of physicians do not comply with clinical guidelines and indications to use PPIs. This irrational prescribing practice is the reason behind the over consumption of this group of medicine, and most likely to cause adverse effects in these patients. Consequently patients are required to treat those symptoms, which appear as a result of side effects. It is appropriate to optimize dietary intake or either consider supplementation of calcium to treat drug induced hypocalcaemia magnesium for hypomagnesemia Iron and B12 to compensate anemia etc and susceptibility to infections like C. difficile associated diarrhea and community acquired pneumonia.

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