The Physiological Aspects of Effective and Safe Proton Pump Inhibitor Therapy for Acid Suppression in Quetta

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Abstract
This research was designed to analyze the in-appropriate use of proton pump inhibitors (PPI) especially in people who are often affected by syndromes of bones, osteoporosis and taking life long PPIs and multiple medications. An increased risk of long-term use of PPI-related adverse outcomes as well as drug-to-drug interactions are discussed in this study. The prescribing proton pump inhibitors for long time use is a common practice now a days. In some cases patients with peptic ulcers have to take the PPI for whole life. The patients used PPIs and there evolved a distress for the strong an...
evidences showed that PPI use could be associated with development of spontaneous bacterial peritonitis.

Table I. Adverse Events Reported in Patients Treated With Proton Pump Inhibitors

| Adverse events unrelated to acid inhibition | Adverse events related to acid inhibition |
|------------------------------------------|----------------------------------------|
| Allergic reaction to drug chemicals      | Pneumonia                                |
| Collagenous colitis                      | Gastrointestinal infection               |
| Acute interstitial nephritis             | Gastric carcinoid tumor                  |
| Chronic kidney disease                   | Gastric fundic mucosal hypertrophy       |
| Drug interaction                         | Changes in gut microbiome                |
| Dementia                                 | Small intestinal bacterial overgrowth    |
| Cerebral ischemic diseases               | Iron deficiency                          |
| Ischemic cardiac diseases                | Bone fracture                            |
| Pneumonia                                | Vitamin B12 deficiency                   |
| Hypomagnesemia                           | Gastric fundic gland/polyps              |
| Gastric cancer                           | Colon cancer                             |
| Spontaneous bacterial peritonitis        | Hepatic encephalopathy                   |
| Drug interaction                         |                                        |

PPI use in patients with liver cirrhosis must be very cautious since there is no evidence of benefit except for downgrading esophageal reflux after sclera therapy. The drugs such as omeprazol, Lansoprazole, rabeprzole, pantaprazole and esenoprazole were found effective in such conditions of GIT and associated soft tissue infections and lowering in stomach pH.

Table II. The frequency of common GERD symptoms in the general population and their percentage of occurrence

| Symptoms               | Frequency  |
|------------------------|------------|
| Heart, burn            | 70–85%     |
| Regurgitational        | 60%        |
| Dysphagiaas            | 15–20%     |
| Angina,like,pain       | 33%        |
| Bronchospasmm          | 15–20%     |

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 (12).

The indication of proton pump inhibitors (PPIs) in clinic levels increases the dangers of bones weakness and decrease in muscular strength (9). A comprehensive prolonged treatments, abandoned indications and therapy replacements are recommended in such conditions (10).

Proton pump inhibitor are exclusive drugs in the administration of acidity related condition. However, simple PPI therapy having no big risk of adverse effects (11, 12). Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium or vitamin B12.

Methodology of the Study

The random sampling method was used to collect data from different hospitals of Quetta, whereas the PPI and drug analysis was done in provincial drug testing laboratory health department, Government of Balochistan, Quetta. Sixteen patients were divided into 4 study groups. Patients included in the study were H. Pylori negative. Qualitative & quantitative analysis of PPIs were performed, acidity sign of relief before and after meals were noted, liver function test (LFT) test for alkaline phosphates was also performed, erythrocytes sedimentation rate (ESR) and Complete blood picture (CBC) were also performed.

Qualitative analysis

Qualitative analysis of PPIs was done in Provincial drug testing Lab., Provincial health department Balochistan, Brewery road Quetta. The drugs and usage ranges were: Omeprazole (20-40 mg), Lansoprazole (20-40 mg), Rabeprzole (20-40 mg), Pantaprazole (20-40 mg), Esenoprazole (20-40 mg).

Study Subjects

The drugs were administered to the subjects suffering from gastro-esophageal reflux disease (GERD), patients taking anticoagulant therapy, symptoms of bleeding, anxiety, stress ulcer prophylaxis (SUP), dyspepsia and anti-inflammatory drugs-associated gastrointestinal symptoms.

RESULTS AND DISCUSSION

Our results showed that the long term use of PPIs results in bone weakness specially vertebilar column and femur. On the other hand in some patients it was noted that long term use of PPIs also resulted in renal impairement and in some cases cardiac vessels may also seem to be involved in degeneration of cardiac muscles. The Table I showing the allergic reactions among the patients suffering from the effects of histamine antagonist and they have a higher degree of non-physiological heat produced through carbohydrate metabolim in the form of higher SGOT or ALT and alkaline phosphate. The frequency of common GERD symptoms in the general population and their percentage of occurrence are given in Table II. Some
Specific PPI formulations should not be selected based on potential risks. The gastric hydrogen potassium ATPase or H⁺/K⁺ ATPase is the proton pump of the stomach. It exchanges potassium from the intestinal lumen with cytoplasmic hydronium and is the enzyme primarily responsible for the acidification of the stomach contents and the activation of the digestive enzyme pepsin (13).

PPIs have become one of the most commonly prescribed drug being the most powerful and effective in treating acid related disorders of GIT. Its long lasting acid suppression is due its prolonged duration of action 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 (12). In July 2005, the State of Tennessee Medicaid Program (TennCare) announced formulary changes for proton pump inhibitors (PPIs) to be implemented in August, 2005. Prior to these changes, pantoprazole was the only preferred PPI, and there were no restrictions to its use. The revised formulary included 3 preferred PPIs (esomeprazole, lansoprazole, and omeprazole OTC), all of which required prior authorization (PA). In order to obtain an approved PA for a PPI, the patient was required to have either (a) a diagnosis of erosive esophagitis, Barrett’s esophagus, Schatzki’s ring, a pathological hyposecrecy condition (e.g., Zollinger-Ellison syndrome, multiple endocrine adenoma), grade III-IV gastroesophageal reflux disease (GERD), non-steroidal anti-inflammatory drug gastropathy, significant gastrointestinal bleed; or (b) another indication for acid suppression therapy (e.g., GERD, hyperacidity in cystic fibrosis, gastric or duodenal ulcer, gastroparesis) with a history of failure of prior therapy with a histamine-2 receptor antagonist (H2-blocker). The internal medicine clinic of a regional medical center implemented an intervention to address these changes in formulary status of PPIs (14).

Adenosine triphosphate (ATP) provides the energy required for the active pumping of protons by the H⁺/K⁺ ATPase (Munson et al, 2000). This enzyme is magnesium-dependent and is found on the secretory membranes of the parietal cells. The sequential phosphorylation and dephosphorylation of the proton pump results in H⁺ secretion in exchange for recycled K⁺. Figure 1.6 represents gastric acid secretion by the parietal cell. This process serves to maintain intracellular pH of about 7.4 in the parietal cell (3). Chloride and potassium ions are transported into the lumen of the canalculus of the stimulated cell via conductance channels. Hydrogen ion is pumped out of the cell into the lumen in exchange for potassium through the action of the proton pump; thus, potassium is effectively recycled. Accumulation of osmotically-active hydrogen ion in the canalculus generates an osmotic gradient across the membrane which leads to outward diffusion of water. The resulting gastric juice contains about 150 mM HC1, 15 mM KC1 and a small amount of NaC1 (2).

Conclusion

In Balochistan, specially in Quetta there is a large number of people who are suffering from acidity. They are usually associated with GERD (gastri intestinal reflux disease and IBS) irritable bowel syndrome. Ultimately they are suffering with side effects of proton pump inhibitors like bone weakness and habitual PPI intake.

REFERENCES

1. Parente F, Cucino C, Gallus S, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. Aliment Pharmacol Ther. 2003;17:1503–6.

2. Wermeling M, Himmel W, Behrens G, Ahrens D. Why do GPs continue inappropriate hospital prescriptions of proton pump inhibitors? A qualitative study. Eur J Gen Pract. 2014;20:174–80.

3. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol. 2012;5:219–32.

4. Gupta R, Garg P, Kottoor R, et al. Overuse of acid suppression therapy in hospitalized patients. South Med J. 2010;103:207–11.

5. Ahrens D, Chenot JF, Behrens G, Grimmsmann T, Kochen MM. Appropriateness of treatment recommendations for PPI in hospital dischargeletters. Eur J Clin Pharmacol. 2010;66:1265–71.

6. Inadomi JM, Fendrick AM. PPI use in the OTC era: who to treat, with what, and for how long? Clin Gastroenterol Hepatol. 2005;3:208–15.

7. Haag S, Andrews JM, Katelaris PH, et al. Management of reflux symptoms with over-the-counter proton pump inhibitors: issues and proposed guidelines. Digestion. 2009;80:226–34.

8. Boardman HF, Delaney BC, Haag S. Partnership in optimizing management of reflux symptoms: a treatment algorithm for over-the-counter proton-pump inhibitors. Curr Med Res Opin. 2015;31:1309–18.

9. Scarpiignato C, Pelosini I, Di Mario F. Acid suppression therapy: where do we go from here? Dig Dis. 2006;24:11–46.

10. Cammarota S, Bruzzese D, Sarnelli G, et al. Proton pump inhibitors prescribing following the introduction of generic drugs. Eur J Clin Invest. 2012;42:1068–78.

11. Richard HH, Carmelo S. Potassium-Competitive Acid Blockers (P-CABs): Are They Finally Ready for Prime Time in Acid-Related Disease? Clin Transl Gastroenterol. 2015;6(10):e119.

12. Anjum A. Rationale use of proton pump inhibitors: Observational study of hospital based prescriptions and role of clinical pharmacist. Pak. J. Pharm. Sci. 2018;31(4):1217-1227.

13. Freedberg DE, Kim LS, Yang YX. Gastroenterology. 2017; 152(4):706-715.

14. Ramsen KL, Sprabery LR, Hamann GL, George CM, Will A. J Manag Care Pharm. 2009;15(4):344-50.

15. Sahoo N, Gu M, Zhang X, Raval N, Yang J, Bekier M, Calvo R, Patnaik S, Wang W, King G, Samie M, Gao Q, Sahoo S, Sundaresan S, Keeley TM, Wang Y, Marugan J, Ferrer M, Samuelson LC, Merchant JL, Xu H. Gastric Acid Secretion from Parietal Cells Is Mediated by a Ca²⁺ Efflux Channel in the Tubulovesicle. Dev Cell. 2017;41(3):262-273.