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 antagonistic effect as a result of its continuous therapy. The first reported proton pump inhibitor was omeprazole and then lansoprazole. The French gastroenterologist Jean Paul Galmiche has anticipated that the unprecedented clinical effectiveness of this medicine would have lead (patients and physicians alike) to dependence, and indeed, this is the case. The study aims to document potential disadvantages and benefits of PPI in patients of Quetta. The results of this study showed that the long term use of PPIs results in bone weakness specially vertiberal column and femur.

Keywords: PPI (Proton Pump Inhibitors), Acid, pH.HCL, GERD

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INTRODUCTION

The therapy of proton pump inhibitor continuous results in onset of peptic ulcer and hepatic problem (1). Low indications or poor acidity signals their use offers little benefit. Patients in hospital often are given on PPIs, often improperly and certainly, inadequate recommendations for PPIs in discharge slip of hospital admitted patients are quite common (2). As the PPIs are now available over any medical store counter (3), patients can have easy access to them and for long phases of time, without seeking medical care (4) and Medication of PPI for long term used by physicians need a care, such as malignancy, that should not be overlooked (5).

Acid Secretion and the Role of the Proton Pump

The proton pump is the final step in the mechanism of gastric acid secretion. When gastric acid secretion is stimulated, there is a morphologic transformation of the membrane of the parietal cell (Helander, 1984). Tubulovesicular membranes, which are prominent in the cytoplasm of the resting cell, diminish in accordance with a 6-10 fold increase in an apical canalicular membrane and the appearance of long apical microvilli. (6). 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 (3).

Acid is produced within the parietal cell from the dissociation of water. The hydroxyl ions formed in this process

rapidly combine with carbon dioxide to form bicarbonate ion a reaction catalyzed by carbonic anhydrase. Bicarbonate ions are then transported out of the basolateral membrane of the parietal cell in exchange for chloride ions. The rapid entry of bicarbonate ions into blood results in a slight elevation of blood pH known as the 'alkaline tide'. 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 HCl, 15 mM KCl and a small amount of NaCl (2).

Once proton pump inhibitor PPI, used by large number of patients for long-term, the proton pump inhibitors, often, may result in bone weakness and sometimes cardiac distress, especially the mature women. Even though PPIs being the ideal anti-secretory drugs and that innovative longer-acting compounds that developed prolonged acid suppression and they stay, no doubt, the PPIs are prescribing in all age group and give very effective result in all available medications.

The PPI initiating 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 represents gastric acid secretion by the parietal cell (5).

Fig. 1. Signaling pathways (that represent gastric acid secretion by the parietal cell) mediate histamine - stimulated ML1 dependent.

TV exocytosis and acid secretion. [Adopted from Niraka S et al., 2017] (15).

Hydrogen ions are secreted against both a parietal cell-to-lumen concentration gradient and an electrical gradient. Thus, HCl secretion by parietal cells is an active energy-dependent process. Parietal cells contain abundant mitochondria to accomplish the active proton transport (7, 8).

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), Rabeprazole (20-40 mg), Pantaprazole (20 -40 mg), Ezenoprazole (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 vertebral column and femur. On the other hand in some patients it was noted that long term use of PPIs also resulted in renal impairment 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 metabolism 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

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
	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 ulcers after sclera therapy. The drugs such as omeprazole, lansoprazole, rabeprazole, 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%
Dysphagia	15-.20%
Angina, like, pain	33%
Bronchospasm	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.

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).

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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 canaliculus 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 canaliculus generates an osmotic gradient across the membrane which leads to outward diffusion of water. The resulting gastric juice contains about 150 mM HCl , 15 mM KCl and a small amount of $NaCl$ (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 (gastric intestinal reflux disease and IBS irritable bowel syndrom. Ultimately they are suffering with side effects of proton pump inhibitors like bone weakness and habitual PPI intake.

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