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Review Article

Adverse Reactions of Proton Pump Inhibitors: A Literature Review

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ABSTRACT

Gastroesophageal Reflux Disease (GRD) is the most common form of esophagitis, where proton pump inhibitors are the most widely used drugs. This study aimed to perform a literature review about the clinical use and adverse reactions of proton pump inhibitors (PPIs). Treatment of GRD evolved in the 1970s, when the first PPI, timoprazole, was discovered and in 1979, omeprazole originated, with a high action on the proton bomb. The most potent drugs in gastric suppression are proton pump inhibitors where they act irreversibly in the proton pump H^+, K^+, - ATPase, the suppression of acid secretion lasts for 24-48 hr. PPIs with prolonged use are associated with changes in the intestinal microbiota, which can be compared to changes seen with antimicrobials, in addition to altering the absorption of iron and Vitamin B_{12} and the metabolism of calcium and magnesium. The population most susceptible to the appearance of the side effects of PPIs is the elderly, age is a factor that predisposes to the appearance of various pathologies and it is necessary to use many medications thus constituting a polypharmacy, in addition, may increase the risks of drug toxicity due to the hepatic metabolism of the elderly being compromised, this is a worrying condition, as it can cause, in addition to the side effects of PPIs, drug interactions, making pharmacotherapeutic follow-up essential, thus being able to make dose adjustments and assess possible drug-related problems and adverse drug reactions.

Key words: Adverse effects, Proton pump inhibitors, Pharmacotherapy, Pharmacovigilance, Reflux diseases.

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INTRODUCTION

Gastroesophageal Reflux Disease (GRD) is the most common form of esophagitis, the lower esophageal sphincter being the main barrier for reflux of stomach contents and having a parasympathetic innervation between the peptidergic fibers of the vagus nerve that releases vasoactive inhibitor peptide (VIP) and it causes relaxation of the smooth muscle of the lower esophageal sphincter. Among the factors that favor the genesis of GRD are pregnancy, obesity, alcohol, tobacco, stress, fatigue, excessive food consumption, hiatal hernia, central nervous system depressant drugs, among others. There are many cases that the cause is idiopathic.[1] The symptoms of GRD are classified as typical (heartburn and regurgitation) and atypical (chest pain, hoarseness, dysphonia, clearing throat, chronic cough, laryngeal spasm).[2]

The most potent drugs in gastric suppression are proton pump inhibitors where they act irreversibly in the H^+, K^+, ATPase proton pump, the suppression of acid secretion lasts for 24-48 hr. These drugs are prodrugs and are activated in acidic media.[1]

Most of the diseases treated with PPIs require a longer period of treatment, in which case the risks that these drugs can bring to health and ensure the safety of the patient in prolonged use must be evaluated. Among the side effects caused by PPIs, some will be mentioned, such as an increased risk of enteric infections, hypergastrinemia, magnesium deficiency, Vitamin B_{12}, iron and calcium.[3] The population most susceptible to the appearance of the side effects of PPIs is the elderly, age is a factor that predisposes to the appearance of several pathological situations and it is necessary to use many medications thus constituting a polypharmacy, in addition, it can increase the risks of drug toxicity due to the hepatic metabolism of the elderly being compromised, this is a worrying condition, as it can cause, in addition to the side effects of PPIs, drug interactions, making pharmacotherapeutic monitoring essential.[4]

Therefore, this research sought to describe the clinical use, pharmacology and adverse effects of proton pump inhibitors.

GASTROESOPHAGEAL REFLUX DISEASE (GRD)

The production and secretion of gastric acid is a constant process that encompasses several factors for the release of hydrogen (H^+) through parietal cells, among the factors is acetylcholine (ACh), histamine and gastrin both act in the regulation of production of acid secretion from the esophagus. However, it is necessary to stimulate some structures for the production of gastric acid, these are arranged in the central nervous system (CNS) such as the hypothalamus, the dorsal motor nucleus of the vagus nerve and the nucleus of the solitary tract.[5]

According to Brunton (2012)[5], when the levels of H^+ are high, a defense mechanism must be obtained to protect the esophagus and stomach. In this way, the production of secretion of cytoprotective mucus and bicarbonate is active, establishing a defense in the protection of gastric

epithelial cells. The mucus when secreted is soluble, however it becomes an insoluble form to delay the diffusion of ions, thus preventing lesions by macromolecules (pepsin) in the mucosa.

Under normal physiological conditions, it is the function of the upper esophageal sphincter to prevent air from entering the upper esophagus, whereas the lower esophageal sphincter prevents the acidic gastric contents from entering the lower esophagus. Thus, when food is eaten, both are opened to allow their passage, but there are some factors that alter the physiology of the esophagus, which is constituted by the stratified pavement epithelium, where it is vulnerable in an acidic environment causing injuries in circumstances such as increased abdominal pressure and decreased tone of the lower esophageal sphincter, among the factors that favor the emergence of GRD include pregnancy, obesity, alcohol, tobacco, stress, fatigue, excessive food consumption, hiatus hernia, central nervous system depressant medications, among others. There are many cases, the cause of which is idiopathic.[1,6]

Among the typical symptoms of GRD, pyrosis (burning sensation) is the change in the pH of the esophagus, which is more frequent in adults and as the years go by this symptom increases, in addition to the common factors that interfere in the symptoms such as fatty foods, lying down after meals, spicy and citrus foods, coffee, soft drinks, smoking, weight gain, stress, another typical frequent symptom is regurgitation (food regression).[2,7]

Patients with atypical symptoms most often do not have typical symptoms, making clinical diagnosis of GRD difficult, among these symptoms is chest pain, otorhinolaryngological symptoms (hoarseness, dysphonia, throat clearing, chronic cough, laryngeal spasm).[2]

PROTON PUMP INHIBITORS (PPIS)

In the last few years it was verified that the use of PPIs has had a great increase, with this, health expenses and the possible adverse effects with their prolonged use have increased.[8] In the beginning of the 20th century, the treatment of gastroesophageal reflux disease was based on the use of foods with basic pH (alkaline), such as purees, milk and eggs, later it was discovered that sodium bicarbonate had a result satisfactory in improving the symptoms of GRD, but was not sure about complications.[9,10]

According to Brunton (2012),[3] the most potent drugs in gastric suppression are the proton pump inhibitors where it consists of H^+, K^+, - ATPase, these drugs are prodrugs and are activated in acidic media, for this reason it is indicated that administer the medication 30 min before the meal, if administered together the medication may not have its expected clinical effectiveness.

Bearing in mind that PPIs are prodrugs, they are absorbed and pass to systemic circulation later, diffusing in the parietal cells of the stomach and accumulating in acid secretory canaliculi, where it is activated by the formation of a tetracyclic sulfonamide catalyzed by protons, retaining the drug so that it cannot diffuse again through the canalicular membrane. Subsequently, the activated form binds covalently to sulfhydryl groups of cysteines in H^+, K^+, -ATPase, this energetic bond is so strong that it irreversibly inactivates the pump.[5]

According to the PPI pharmacokinetics, after being absorbed, plasma proteins are bound and after undergoing the biotransformation process by cytochrome enzymes specifically, CYP2C19 and CYP3A4 and consequently are excreted.[5]

Therefore, the suppression of acid secretion lasts for 24-48 hr, due to the irreversible bonding and it only resumes when new molecules are produced.[5] Although the drugs in the IBP's class contain pharmacokinetic differences, they have a similarity between them, both reduce up to 95% the daily production of gastric acid.[11]

COMPLICATIONS OF THE CONTINUED USE OF PROTON PUMP INHIBITORS

Most of the diseases treated with PPIs require a longer period of treatment, in these cases one must evaluate the risks that these drugs can bring to health and ensure patient safety in prolonged use. Recently, the relationship between the chronic use of proton pump inhibitors and possible side effects has been investigated, however, there is no complete evidence. Among the side effects caused by PPIs, some are mentioned, such as the increased risk of enteric infections, hypergastrinemia, magnesium deficiency, vitamin B12, iron and calcium, which will be the focus of the present work.[3]

PPIs with prolonged use are associated with changes in the intestinal microbiota, which may be more pronounced than the changes seen with antimicrobials.[12]

One of the causative agents of these infections is Clostridium difficile in which its vegetative form is destroyed in an acidic medium, however, the constant use of PPIs makes the pH of the esophagus and stomach more alkaline and promotes the proliferation of these bacteria.[13]

Among the functions of gastric acid is the elimination of pathogens. Normally acid secretion in the stomach corresponds to a pH of 1.4, however people who have pathology with gastroesophageal reflux disease need a gastric pH> 4 to stop the symptoms.[14]

One of the most common conditions is hypergastrinemia. Gastrin is a hormone produced in the gastric antrum by G cells. It has a trophic effect on enterochromafim-like (ECL) cells that have great relevance in the production of gastric acid. ECL cells produce histamine-2 where it acts on the histamine receptors of parietal cells, stimulating acid secretion.[15,16] PPI therapy results in an alkaline pH, leading to hyperplasia of ECL cells through gastrin overproduction. In a study conducted with rats using PPIs for life, they developed dysplasia of ECL cells and neuroendocrine tumors (NET).[17]

Hypomagnesaemia has also been mentioned. Magnesium (Mg) is essential for cells with ATP to function properly, thus being a cofactor, for example in the Na-K-ATPase and H-ATPase pump. The decrease in serum magnesium levels can lead to some complications, such as depression, muscle weakness, seizures, among others[18,19]

A few years ago, IBP's drugs were associated with a decrease in serum magnesium concentrations.[18,20] As of 2007, the British National Formulary used PPIs as a predisposing factor for hypomagnesaemia. In 2011, the Food and Drug Administration (FDA) informed that the use of PPIs, mainly in chronic use, leads to a decrease in serum Mg levels. Despite this, this relationship is still not well known.[19,21]

Reports of decreased absorption of Iron and Vitamin B_{12} are also reported. Iron has two ways to be purchased, the first is through foods that contain iron, this is responsible for 32% and the other is due to lysis of red blood cells, being reused the iron present in it, this process has the greatest impact on in relation to obtaining iron 66%. The absorption of iron due to red cell lysis increases with gastric acidity and PPIs decrease this acidity, consequently interfering with iron absorption. When PPI therapy is longer than 1 year, the decrease in hemoglobin is already noticeable, resulting in the emergence of anemia.[22-25]

Vitamin B_{12}, plays an essential role for the effective functioning of the central nervous system and hematological functions. It is acquired only through food and absorbed in an acidic medium, so as PPIs cause gastric suppression, consequently it reduces the absorption of Vitamin B_{12}.[26,27] Studies have shown that the PPIs in chronic use, mainly, the elderly have a cognitive impairment having a potential in the development of Alzheimer's disease.[26,28]

As for calcium deficiency, bone tissue is composed of connective tissue formed by a mineral phase, consisting of crystals of calcium phosphate. The cells that make up bone tissue are constituted in two different ways: Osteoclastic cells, associated with resorption and osteoblastic cells, which integrate bone matrix formation and mineralization.[29,30]

The cells that are part of the remodeling of bone tissue and the absorption process are osteoclasts, these have proton pumps where they are used to produce an acidic medium through the release of H^+ and this process helps in the decalcification of the bone matrix. PPIs also act in the inhibition of the osteoclast proton pump, thus interfering with bone metabolism, increasing the risks of osteoporosis, alteration of bone density and structure and mainly pelvic fractures.[31]

Then, the population most susceptible to the appearance of the side effects of PPIs is the elderly, since age is a factor that predisposes to the appearance of various pathologies and it is necessary to use many medications, thus constituting a polypharmacy, in addition, it can increase the risks of drug toxicity due to the hepatic metabolism of the elderly being compromised, this is a worrying condition, as it can cause, in addition to the side effects of PPIs, drug interactions, making pharmacotherapeutic monitoring essential and thus making adjustments doses and evaluate possible problems related to drugs and adverse drug reactions.[4,32]

CONCLUSION

From the foregoing it appears that the proton pump inhibitors are safe and effective drugs, when used rationally in clinical practice, however as well as in the use of any other drug, one must be special because they are cautious in their use, taking into account in view of the care with its adverse effects and drug interactions, especially in elderly patients who naturally present changes in physiological functions and, as a rule, use polypharmacy.

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