

Pharmacogenetics of Proton Pump Inhibitors: Short Review

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ABSTRACT

Background: Proton pump inhibitors are substituted benzimidazoles compounds, they are used as agents for the treatment of acid-peptic diseases. These compounds are metabolized by several enzymes, the genetic variations in these enzymes were thought to influence the pharmacogenetics of the proton pump inhibitors and in turn influence the outcome of the patients.

Aim: To highlight the pharmaco-genetics of proton pump inhibitors

Methods: Scientific websites were used to search for articles such as Pubmed and Google Scholar. Several keywords were used to obtain all possible articles concerned with the subject.

Results: We reviewed 6 articles about the current subject, there were few articles about the pharmacology of proton pump inhibitors.

Conclusion: Few studies have focused on the pharmacogenetics of proton pump inhibitors and most of them were trials, also there were no previous review articles studied this subject.

Keywords: PPI, Peptic ulcers, Genetic variations, Pharmacogenetics.

INTRODUCTION

Proton pump inhibitors (PPIs) are agents that considered as a major advance in the treatment of acid-peptic diseases. They are the most common class of medication prescribed in the primary care setting^[1]. These agents ranked in the top of 10 national health-related drug expenditures in US in 2015^[2]. The introduction of first PPI which was omeprazole (Prilosec), was in 1989, after that several PPIs became available^[1] including rabeprazole, pantoprazole and lansoprazole^[3]. PPIs are selectively and irreversibly inhibit the gastric hydrogen potassium adenosine triphosphatase (H⁺/K⁺-ATPase) pump mechanism in gastric parietal cells^[3,4]. PPIs are used for the treatment of Barrett's esophagus, Zollinger-Ellison Syndrome, gastroesophageal reflux disease and peptic ulcer disease^[3]. The pharmacological effects of most drugs are dependent on both the pharmacokinetic process and pharmacodynamics^[5]. These processes in turn occur at variable levels in each individual, and the major determinant of this variability is genetics^[5]. In the present review we highlighted the pharmacogenetics of PPIs as well as uses of PPIs.

MATERIALS AND METHODS

In the current review, we used the internet to get the articles related to our subject, we used several key words including PPI, PPI metabolism, Pharmacogenetics of PPI, PPI uses. Scientific web sites were used for researching for articles such as Pubmed, Google Scholar and research Gate. We obtained 17 articles, 11 of them were excluded as

they didn't involve the main points we searched for, while 6 articles were reviewed. These 6 articles were published between 2002-2017.

The study was done after approval of ethical board of King Fahad Central Hospital.

1. Pharmacology of Proton Pump Inhibitors (PPI):

PPIs are substituted benzimidazoles compounds which are administrated either as capsules or enteric-coated tablets which pass through the stomach reaching to proximal small bowel where they are absorbed^[1]. After absorption, PPIs have short plasma half-life which ranges from one to 2 hours, while duration of action is much longer as they have a unique mechanism of action^[1].

As PPIs are lipophilic weak bases, they cross the parietal cell membrane and then enter the acidic parietal cell canaliculus. PPIs becomes protonated in the acidic environment, this results in producing the activated sulphenamide form of the drug which has the ability to bind covalently with the H⁺/K⁺-ATPase enzyme, this in turn results in irreversible inhibition of acid secretion by the proton pump^[6-8]. Rabeprazole (Aciphex) differs from other PPI, where it forms a partially reversible bond with the proton pump, it is also activated at a broader range of gastric pH, so it has more effect on acid-suppressing than the other PPIs^[6,7,9].

For resuming acid secretion, the parietal cell must activate resting pumps or produce new proton pumps^[6,7].

2. Proton Pump Inhibitors uses:

2.1 Gastroesophageal reflux disease (GERD)

This disease can be diagnosed by regurgitation, dysphagia and heartburn (pyrosis) [1,5]. Classic GERD symptoms of patients can be treated by modification of lifestyle and patient-directed antacid or acid suppression therapy [10]. Patients with GERD are likely to respond to PPIs as they are highly effective acid suppressants. It was assumed that patients who had typical symptoms and responded to PPI therapy have GERD [10,11]. There are 2 common approaches about the initiation of GERD treatment, but no one was approved to be superior, so the physician determines the most appropriate one [1]. Step-up therapy and Step-down therapy are the 2 approaches; the former begins with standard-dosage or over-the-counter H₂ blockers and titrates to symptom control, while the later starts with once- or twice-daily PPI therapy and the dosage is changed or decreased to the lowest form of acid suppression which will control the patient's symptoms [10].

2.2 Peptic Ulcers:

Peptic ulcers usually occur as a result of *Helicobacter pylori* infection or therapy with non steroidal anti-inflammatory drugs (NSAIDs) [1]. The recurrence of peptic ulcer disease can be done by the eradication of the infection [12]. The current treatment for *H. pylori* is based on a triple therapy which is composed of two antibiotics and PPIs. This regimen is effective in 70-90% of patients [5]. PPIs showed shorter healing time, faster symptom relief and superior healing rates that were attained with H₂ blockers in patients with ulcers [7-9]. It was stated that PPIs have the ability to heal peptic ulcers that may be refractory and also has antimicrobial activity against *H. pylori* in vitro [1]. PPIs suppress *H. pylori* in vivo only, while antibiotics alone are ineffective in *H. pylori* eradication, so combination of antibiotic therapy and adequate acid suppression is necessary for the eradication of *H. pylori* [7-9]. The combination of PPI and antibiotics resulted in decrease of the recurrence rate of peptic ulcers, where it was found that the recurrence rate was less than 10% by using this combination [7,13]. Peptic ulcers that caused by NSAIDs occurs as NSAIDs weaken gastroduodenal mucosal defenses and inhibit prostaglandin synthesis [1]. Also, they cause disturbance in the mucoprotection [14]. Complicated or large ulcers can be treated by PPIs [7,15].

3. Pharmacogenetics of Proton Pump Inhibitors:

Pharmacogenomics involves the genomic analysis which can be applied to predict the patient's response before treatment [16]. Cytochrome P450 is

the most important mechanism of drug metabolism in the body [16]. Extensive hepatic biotransformation of PPIs occurs by the cytochrome P450 (CYP) system [17-20]. Several enzymes are involved in drug metabolism and they include CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5/7 [5]. Both CYP2C19 and CYP3A4 are the main isoenzymes that involved in the metabolism of the PPIs [21]. CYP2C19 acts on omeprazole and lansoprazole by initial hydroxylation, while it has lesser extent on the demethylation of pantoprazole and rabeprazole, which are the steps that produce metabolites without antacid activity [5]. However its action depends on the dose, at high omeprazole concentrations, it acts as an alternate enzyme as omeprazole has a 10-fold lower affinity for CYP3A4 [20,22-27]. Both CYP2C19 and CYP3A4 act on lansoprazole and rabeprazole [20,25]. Sulphotransferase is a non saturable enzyme outside the CYP system, however it acts on pantoprazole as pantoprazole has lower affinities for both previous enzymes [20, 28-31]. The function, structure and expression of most enzymes involved in metabolism and drug transportation may be influenced by the presence of genetic variants, this can lead to modification in the intended therapeutic effect or even appearance of adverse effects [5]. Molecular alteration results in genetic variations, the molecular alteration includes single nucleotide polymorphism, gene duplication or gene deletion [3]. The most common variants and targets of pharmacogenetic tests are the single nucleotide polymorphisms (SNPs), which refers to change in a single base in the nucleotide sequence [5]. It was suggested that CYP2C19 genetic polymorphism can result in a significant phenotypic variation in the activity of this isoenzyme, hence the metabolism and efficacy of the PPIs change either [27]. There were 21 variants of CYP2C19 assigned from *1 to *20. The wild type allele is CYP2C19*1, while CYP2C19*2 is a variant allele which contains 681G>A on exon 5 that causes a splicing defect, it is the main genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans [5]. CYP2C19*3 carries the 636G>A SNP, this leads to a premature stop codon in exon 4. Both CYP2C19*2 and *3 are null alleles, which cause absence of enzymatic activity [32]. These two alleles are responsible for the majority of PMs of CYP2C19 [33]. In a systemic review [3] the authors concluded that the correlation of CYP2C19 polymorphism on PPIs pharmacogenetic regarding the clinical outcomes of PPI therapy wasn't clear. Several previous studies of dual therapy with a proton pump inhibitor and amoxicillin demonstrated that differences in CYP2C19 genotypes were associated with failure in

eradication of *H. Pylori* [34-37]. Another study [38] showed that variations in CYP2C19 genotype affected the eradication rates of lansoprazole-based therapy. GERD is refractory to PPI therapy in 10% of patients and the most important reason for that is differences in the efficiency of the metabolism of the drug [5]. It was also referred that the genotype is also crucial for the nocturnal acid bouts, which are influential factors in the treatment outcome. These intrusions are more frequent in rapid metabolizers, this resulted in a suggestion for patients who were refractory to standard doses of PPI to receive an increased dose [39,40]. Pharmacogenetics also influences the safety profile of PPIs in case of GERD where it requires long treatment periods [5]. Risk of hyperplasia of enterochromaffin-like cells, which is related to the development of carcinoid tumors has been reported [41].

CONCLUSION

Proton pump inhibitors are agents that are effective in treating peptic ulcers regardless their causes as they are effective antacids. The pharmacogenetics of these agents are influenced by the genetic variations of the enzyme that metabolize them, so the outcome of patients may differ as a result of the genetic variations. There are scarcity studies that were conducted on the proton inhibitors pharmacogenetics and most of them were trials and showed unclear results. It is recommended to establish studies which focus on the pharmacogenetics of proton pump inhibitors which could help in the prediction of the outcome of patients .

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