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Interaction between Proton Pump Inhibitors and Antiplatelet Therapy

Fawaz Tawhari[1], Mohammed Kariri[1], Yahya Addarbi[1], Ibrahim Tawhari[2]
1-Jazan University College of Pharmacy, 2-University of Utah Health Care

ABSTRACT

Background: proton pump inhibitors are agents that inhibit the final step in gastric acid formation. They are available in oral forms or intravenous forms. Proton pump inhibitors can be used in case of gastric ulcer. Antiplatelet therapy is a medication that acts as cardiovascular therapy as it is used in platelet inhibition. Some antiplatelet agents may case ulcer and proton pump inhibitors may become necessary for ulcer treatment, the use of this combination may cause adverse effects for patients.

Aim of the work: this study aimed to investigate the interaction between proton pump inhibitors and antiplatelet therapy. **Materials and methods:** we used the internet to obtain articles about this subject, we used Google scholar, Pub Med and Research Gate to find the articles.

Results: we obtained 44 articles, only 11 were included and we excluded 31 articles as they have either irrelevant title or content.

Conclusion: interaction between proton pump inhibitors and antiplatelet therapy was conflicted. The data available were from randomized studies or trials, patients inclusion criteria, methods and outcome differ between the various studies, also the clinical data were limited.

Keywords: PPIS, antiplatelet therapy, aspirine, clopidogrel.

INTRODUCTION

Proton pump inhibitors (PPIs) are common medication that used in primary care sittings for the treatment of acid-peptic diseases [(1).] PPI was found to be effectively reduced the gastrointestinal bleeding risk in the patients who require dual antiplatelet therapy (DAPT) [(2)].It was recommended in guidelines to use PPI in high-risk patients requiring antiplatelet therapy as a prophylactic [(3)] , but there was a concern about possible adverse effects as a result of drug interaction between PPI and antiplatelet [(4).] Potential pharmacological interaction between these agents was supported by early preclinical data, however clinical data were limited [(4)].

MATERIALS AND METHODS

In this review, we used the internet to search for articles related to the present subject. Key words such as proton pump inhibitors, interactions of PPIs, antiplatelet therapy and interaction of antiplatelet therapy. We found 44 articles, 33 of them were excluded as they were of irrelevant title or content and 11 were included. The included articles were published between 2002 and 2017.

The study was approved by the Ethics Board of Jazan University.

DISCUSSION

Proton pump inhibitors; definition:

PPIs are highly selective potent inhibitors for H^+, K^+ adenosine triphosphate (ATPase) enzyme, this enzyme catalyzes the final step in the secretion of the gastric acid [(5).] The basic chemical structure of PPIs consists of substituted pyridine ring and substituted benzimidazole ring, they are connected together by methylsulfinyl chain [(6)].

Proton pumps inhibitors, types and uses

PPIs are available in an oral formulation such as omeprazole, rabeprazole, pantoprazole, esomeprazole and lansoprazole**.** Intravenous PPIs also are available for those who are unable to administrate tablets or capsules [(5).] PPIs are administrated in the form of capsule with delayed release gelatin which contains enteric-coated granules (lansoprazole and omeprazole) or tablets with delayed-release (pantoprazole and prazole) [(7-11).] Using of intravenous PPIs included conditions related to acid (gastroeosophageal reflux disease), hypersecretory states (Zollinger-Ellison syndrome) and patients who were unable to take oral form [(5).] Also, they can be administrated in other cases such as stress related to mucosal bleeding, prevention of acid aspiration syndrome and peptic ulcer bleeding [(12-14)].

Action of Proton pump inhibitors:

All PPIs have short plasma half-life, but they have long duration of action as they have a unique mechanism of action [(1)]**.** PPIs are prodrugs that require acidic environment to become protonated and convert to the active form [(15).] As PPIs are lipophilic weak bases, they cross the parietal cell membrane and then enter the acidic parietal cell canaliculus [(1).] These acidic conditions make PPIs protonated, so they produce the activated form of sulphonamide of the drug that covalently bind to

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H^+/K^+ ATPase enzyme, this in turn makes acid secretion by the proton pump to be irreversibly inhibited [7,16,17]. The parietal cell can resume acid secretion either by activating resting pumps or produce new proton pump [7,17]. Rabeprazole forms partially reversible bond unlike other PPIs [1].

Side effects of Proton pump inhibitors

The most common adverse effects of PPIs included diarrhea, abdominal pain, headache and nausea; these adverse effects-except for diarrhea-aren't associated with age of patient, duration or dosage of treatment [18,19]. These adverse effects weren't severe; however, PPIs were contraindicated if patient had history of hypersensitivity and caution should be taken with patients with severe hepatic diseases [1].

Anti- platelet uses and Types

Platelet inhibition is considered as the cornerstone of cardiovascular therapy, where platelets have a role in the genesis of acute ischemic events [20]. According to mechanism of action, there are 4 classes of antiplatelet drugs, the first class is $P2Y_{12}$ receptor blockage such as Clopidogrel, Ticlopidine, Prasugrel, Elinogrel, Cangrelor and Ticagrelor . The second class is Cyclooxygenase enzyme inhibition, this involves aspirin, and the third class is PAR-1 blockage which includes Terutroban, E5555 and SCH-530348. The fourth and last class inhibits either Phosphodiesterase (PDE) such as Dipyridamole or PDE III such as Cilostazol. Cangrelor is administrated intravenously, Elinogrel is administrated either orally or interavenously, while the other agents are administrated orally [21]. In this review we will focus on clopidogrel and aspirin as the majority reports were about them.

Clopidogrel

Clopidogrel is an oral prodrug which is derived from thienopyridine. It prevents the binding of adenosine diphosphate (ADP) by blocking of platelet P2Y12 receptors irreversibly, hence ADP-dependent activation of GpIIb-IIIa occurs which is the major platelet receptor for fibrinogen. Oxidation of 2 steps is required for activation of this prodrug, this oxidation is performed by hepatic cytochrome P450 system (specifically by CYP2C19) [20].

Aspirin

Aspirin is an oral drug which rapidly absorbed after administration from the upper GI tract, its peak level occurs during 30 to 40 minutes after ingestion [22]. Aspirin exerts its effect on platelet by permanent inactivation of a key platelet enzyme (cyclooxygenase [COX]) [23]. The generation of new platelets is the way to reverse its effect [24]. Inhibition of COX by aspirin is taken place by aspirin diffusion to the catalytic site for the enzyme from the COX channel within the membrane, then acetylation of serine residue occurs, this in turn prevents arachidonic acid from accessing to the catalytic site of the enzyme [25]. Increase the risk of bleeding complications is the major adverse effect of aspirin [26,27], especially in GI tract [28].

Anti- platelet action

Dual antiplatelet therapy (DAPT) involves two main pathways mechanism; first via thromboxane A2 formation which inhibits cyclo-oxygenase, the formation of thromboxane A2 occurs by the action of aspirin, the second pathway includes the action of drugs family (ticlopidine, prasugrel, cangrelor, clopidogrel and ticagrelor) which inhibit the ADP-activated surface receptor P2Y12 [20]. Antiplatelet therapy is the standard of care for reducing the risk of ischemic cardiovascular (CV) events in patients with acute coronary syndromes (ACS) [29]. In clinical guidelines, it was recommended to use antiplatelets for the management of ACS, especially aspirin and/or a thienopyridine for secondary prevention of mortality, cardiac-related events and stent-related thrombosis [30-32].

Interaction between proton pump inhibitors and anti-platelet drugs

Patients with heart disease have the risk of gastrointestinal (GI) bleeding and the risk increases by the use of antiplatelet agents [33]. Previous GI bleeding and history of ulcers are very important risk factors [34]. Reduction of the GI bleeding risk in patients taking antiplatelet agents can be performed by healing of ulcers and erosions; this can be done by the action of PPI [33]. It was found from observational and randomized clinical trials that using of PPIs in patients who administrated antiplatelet therapy was associated with a significant reduction in the risk of ulcers, GI bleeding and erosions [2,35-38]. The data about the interaction between PPIs and antiplatelet drugs come from analysis of randomized controlled trials or cohort studies as it is very difficult to adjust for residual confounding factors and condition of the studies [33]. The inclusion criteria of patients differ between the different studies as well as measured outcome and analysis methods [33].

Interaction between proton pump inhibitors and clopidogrel

The most commonly used dual antiplatelet is clopidogrel [33]. Both PPI and clopidogrel share the same metabolic pathway via the CYP2C19

cytochrome P450 enzyme, their interaction can reduce the availability of the clopidogrel active form and as a result, this reduces platelet inhibition [(39).] Also, it was stated that PPIs may prevent the activation of clopidogrel and this leads to increase risk for adverse cardiovascular events [(40-42).]

The Food and Drug Administration warned about this interaction which lowers the antiplatelet effect regarding simultaneous use of these agents [(43).] Several clinical studies showed conflict results about the effect of PPI on long-term ischemic outcomes in patients treated with clopidogrel [(2,8,44-50).] It was mentioned that the increased risk for cardiovascular events was in the range of 25% to 80% in the studies which investigated patients who received PPI and dual antiplatelet therapy [(33).]

There were several meta-analysis and reviews showed that there was no significant difference for increasing risk of diseases by the co-administration of PPIs and clopidogrel [(48,51-53).] A large case control study was conducted to compare the incidence of GI bleeding between the combination of PPIs and clopidogrel therapy and cotherapy alone in 2779 patients with confirmed upper GI bleeding and 5532 controls. It was found that in case of PPI-clopidogrel combination, the relative risk of GI bleeding was lower than in case of clopidogrel therapy alone, which suggests the role of PPI cotherapy in reducing the risk of GI bleeding [(34,54).] It was reported in 2 meta-analysis that there was no association between the use of PPI with clopidogrel and mortality of patients [(55,56)].However, data about safety and efficacy at long term are conflicted [(57)].

Interaction between proton pump inhibitors and aspirin

Aspirin now become the first-line antiplatelet drug in the setting of both secondary cardio- and cerebrovascular prevention [(58).] Although aspirin act for cardiovascular protection, it is the most contributors to mortality related to GI bleeding [(59).] Cardiovascular patients who administrate aspirin require antiulcerant co-treatment to tolerate aspirin [(58).] GI bleeding is life threatening particularly in patients with acute coronary syndromes [(60)] now, using of PPI is a recommended strategy for gastrointestinal bleeding prevention during antiplatelet therapy [(34,61).]

There were concerns about interference between PPIs and the bioavailability and absorption of aspirin, where gastric acidity is altered [(33).] However, it was showed the opposite by small studies in which patients treated with low dose of aspirin (75-100 mg) and PPI [(62,63).] Interaction results between PPIs and aspirin are conflicted **[58]**. Several studies in very small cohorts [(62,64,65)] suggested that PPIs didn't attenuate the effect of aspirin on platelet aggregation, however an association was found in patients with coronary artery disease [(63).] Another study [(66)] on the clinical importance of combination between PPIs and aspirin showed that using of PPIs was related to increased risk of adverse cardiovascular events in patients with first time myocardial infarction who treated with aspirin. A recent randomized cogent trial presented strong evidence that in patients on dual antiplatelet therapy (aspirin +clopidogrel), PPIs reduce gastrointestinal bleeding complications. This trial revealed that the risk of gastrointestinal bleeding can be reduced without increasing cardiovascular event rates or mortality [(2)].

CONCLUSION

In this review we concluded that all studies focused on interaction between PPIS with either aspirin, clopidogrel or both. We couldn't find any study on the interaction between PPIs and other types of antiplatelet agents. The data about PPIs interaction with aspirin and clopidogre were based on randomized controlled trials or cohort studies, also the inclusion criteria of patients in the study differed between different studies as well as the analysis methods and outcome of patients. All the previous factors made the results to be conflicted, particularly in the long term, so further studies are needed.

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