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Research Article

Indiscriminate Use of Proton Pump Inhibitors and Possible Cardiovascular Risk

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ABSTRACT
We have witnessed rise in the indiscriminate use of over the counter preparations of Proton pump inhibitors. Proton pump inhibitors are known to cause nutritional deficiencies, rebound acid hypersecretion and achlorhydria, acute interstitial nephritis, gastric carcinoid tumour. Similarly, co-prescription with clopidogrel leads to various cardiovascular effects even among normal individuals. Though PPI may increase the risk of arrhythmias and enhance cardiovascular risk on high dose parenteral use of PPI, the role of PPI in modifying NO activity will definitely enhance the risk of cardiovascular events manifold among the general population. Hence, there is a definitive need to conduct cross sectional, prospective and community based trials to uncover the human applicability of the observation by these researchers and increase the pharmacovigilance for these class of drugs.

Keywords: Proton pump inhibitors, Cardiovascular risk, Indiscriminate

INTRODUCTION

Proton pump inhibitors (PPI) have rapidly become an indispensible part of the management of gastro esophageal disorders since their introduction about two decades ago. Similarly, we have witnessed rise in indiscriminate use of over the counter preparations of PPI. Co-prescription of PPIs with NSAIDS have also accounted for steep rise in demand of PPIs across the various continents. Proton pump inhibitors are one of the most frequently prescribed classes of drug in the world owing to their combination of high efficacy and low toxicity. Medical field has witnessed a substantial rise in incidence of the acid dyspepsic group of disorders due to stress, harmful dietary habits and sedentary lifestyle. Similarly, there has been proportional increase in prescriptions of PPIs. In 2009, more than 119 million PPI prescriptions were filled in the United States, accounting for nearly $14 billion dollars in prescription PPI sales, in addition to billions more in over-the-counter (OTC) sales[1]. Steep rise has also been witnessed in PPI prescriptions among pediatric patients of age less than 1 year increased 7.5-fold from 1999 to 2004[2]. In 2006, expenditure on these drugs was £425m (€595m; $872m) in England[1] and £7bn globally. This can be attributed to the consistent rise of 15-20% per annum in the prescriptions of PPI since 2000. Many observational studies have shed light on this old problem of over prescription of PPI in both primary care and hospital based settings. It has been consistently observed that between 25% and 70% of patients taking these drugs have no appropriate indication. Similarly, in hospital inpatients taking proton pump inhibitors in Australia, Ireland, and the UK, 63%, 33%, and 67% of patients did not meet their country's criteria for taking the drug. Over-use prior to endoscopy, use in patients who do not fit the approved criteria, and prescribing for indications in which 'less powerful' agents should have been sufficiently effective for the patient's symptoms could be assessed to be the reasons for this trend[3]. PPIs are basically prodrugs and require activation by parietal cells of stomach to form positively charged active drugs and they subsequently bind irreversibly to proton pump there by inhibiting acid secretion. This mechanism of action makes them drug of choice for management of gi disorders like dyspepsia, GERD, H pylori infection and others. It is also used in prophylaxis and treatment of peptic ulcers in ICU settings and among the high risk patients on co- prescription of aspirin, NSAIDS, antiplatelets, anticoagulants etc. Due to their irreversible binding with the proton pump, though their plasma half life is on average 1-2 hours yet their duration of action lasts for 3-4 days – hit and run drugs[4]. Multitude of studies in past years have highlighted various adverse effects of PPI like nutritional deficiency (B12 and Mg), rebound acid hypersecretion and achlorhydria, acute interstitial nephritis, gastric carcinoid tumour, cardiovascular risk with clopidogrel, bone fractures,

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anaphylactic reactions with parenteral PPI, enteric infections like clostridium difficle, pneumonia in ICU settings[4]. Use of PPI, either as a single drug or as a co-prescription with clopidogrel, have both been observed to modify the cardiovascular risk among diseased or health individuals. Conflicting evidence has come to light regarding the enhanced cardiovascular risk among people using PPI. Researchers have raised concerns regarding enhanced cv risk among patients on co- prescription with PPI and clopidogrel. The mechanism which was initially thought to be the CYP450 2C1q.2 has now been proven to be the genetic polymorphism. Such polymorphism leads to reduced function of CYP2C1q.2 allelle common among asian americans (51%) and African American is responsible for impaired clopidogrel activity.[4] Similarly PPI use among the patients discharged after first-time myocardial infarction was observed to be associated with increased risk for adverse cardiovascular outcomes after discharge, regardless of clopidogrel use for myocardial infarction. The authors have concluded that Dual PPI and clopidogrel use was not associated with any additional risk for adverse cardiovascular events over that observed for patients prescribed a PPI alone. These contradictory findings were attributed to the unmeasured confounders such as smoking, lipid levels, body mass index, and left ventricle ejection fraction[5]. In a study conducted by Schillinger w et al, it was observed on preliminary in vitro analysis that PPI like pantoprazole (parenteral) had negative ionotropic effect on human and rabbit myocardium. This study refuted the possibility of negative inotropy of pantoprazole in myocardium as a consequence of H_/K_-ATPase inhibition. It supported the possibility of effects of pantoprazole on intracellular Ca2_ homeostasis and myofilament Ca2_ responsiveness, as mechanisms of the altering myocardial contractility. The combination of reduced SR calcium uptake and reduced Ca2_influx explained the reduction in SR Ca2_ content observed and raised diastolic [Ca2]I. The negative inotropy of pantoprazole was dose dependent as observed at 10 _g/mL mainly resulted from decreased intracellular [Ca2_] and at the higher dose (40_g/mL), resulted from depression of myofilament responsiveness. Such effect of PPI on myocardium would definitely have special implications among patients with compromised cardiovascular health due to blunting of cardiovascular response. But surprisingly a follow up study by same authors among healthy human volunteers failed to demonstrate the negative ionotropic effect on myocardium. Though, administration of ultra high dose among people may affect the myocardium by altering the contractility[6]. PPI are known to inhibit intestinal absorption of magnesium leading to hypomagnesaemia. Elie El-Charabaty et al conducted a study to assess the association between the use of PPI, serum magnesium levels, and the incidence of cardiac arrhythmia in a large group of patients admitted to the intensive care unit (ICU) with an acute coronary syndrome and subsequently started on a PPI. It was observed by the authors that such a relation of cardiac arrhythmias and PPI exits. Similarly, a case control study was conducted on 80 patients undergoing an electrophysiological study and found that there was a 4-fold increase in focal arrhythmias in the group of the 40 patients on PPI when compared to the control group not on PPI[7]. Before this controversy could be put to rest a fresh perspective by Ghebremariam Y et al 2013 has highlighted possible enhanced risk of cardiovascular disorders among healthy individuals on long term use of PPI. Preliminary biochemical, cellular, ex vivo and in vitro data revealed the potential PPI and human DDAH interactions which results in increased endothelial and serum ADMA levels. These high ADMA levels lead to impairment of nitric oxide synthase activity. NO has a vital role to play in regulation of vascular tone, inhibition of platelet aggregation and adhesion. Persistent high ADMA levels can enhance the chances of MACE'S and mortality even among normal individuals. These findings are supported by longitudinal community based studies like population study of women Gothenburg, framington off spring study. This can enhance the cardiovascular risk among the general population[8]. There are three known isoforms of NO synthase (NOS)- ENOS (endothelial), NNOS (neuronal) and INOS (inducible). ENOS is endothelial membrane bound enzyme and NNOS and INOS are cytosolic enzymes. L-arginine is required for generation of NO. The conversion of L- arginine to NO is inhibited by some arginine competitor such as nmma-n-mono methyl l-arginine. Enos is necessary for endothelial no generation which relaxes blood vessels and prevents platelet aggregation[9]. Apart from being vasodialator and regulating blood pressure, NO also has a antithrombotic effect. Both endothelial cells and platelets contain Enos which acts via NO-cGMP pathway to inhibit platlet activation an initiator of thrombus formation. NO may have an additional inhibitory effect on blood coagulation by enhancing fibrinolysis via an effect on plasminogen. NO also protects against atherogenesis. A major antiatherogenic mechanism of NO involves the inhibition of proliferation and migration of vascular smooth muscle cells. NO reduces endothelial adhesion of monocytes and leucocytes which are early steps in development of atheromatic plaques. This effect is due to inhibitory effect of NO on the expression of adhesion molecules on endothelial surface[9]. In addition, NO may act as antioxidant blocking the oxidation of low density lipoproteins and thus preventing or reducing the formation of foam cells in vascular walls. Plaque formation is also affected by NO dependent reduction in endothelial cell permeability to lipoproteins. Thus PPI can reverse the various beneficial cardiovascular effects of NO by increasing levels of serum ADMA[9]. PPI is the 3rd most commonly prescribed drug in general practice and pediatric practice alike. Similar to other myriad of side effects, cvs effects among normal individuals warrants attention. Though PPI may also increase the risk of arrhythmias and enhance cardiovascular risk on high dose parenteral use of PPI, the role of PPI in modifying NO activity will definitely enhance the risk of cardiovascular events manifold among the general population. Hence, there is a definitive need to conduct cross sectional, prospective and community based trials to uncover the human applicability of the observation

by these researchers. If this is proved beyond doubt, there will be a need to take definitive steps to enhance pharmacovigilance of these drugs and to monitor the excessive use of PPIs available as OTC preparations. These efforts need to be supplemented with appropriate practice guidelines for primary and secondary care physicians and pediatricians, to avoid indiscriminate prescriptions of PPI. This will reduce the potential yet modifiable cardiovascular risk among the general populations.

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