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Proton-pump inhibitors and risk of renal disease

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ABSTRACT

Proton pump inhibitors (PPIs) are one group of drugs that inhibit gastric acid secretion by binding irreversibly to the gastric proton pump. This paper aimed to review the impact of PPIs on kidney function and structure by presenting the updated information in this regard. In this review, we summarize in electronic databases including Google Scholar, EMBASE, MEDLINE, Scopus and EBSCO during the period of 1980 to 2017 by using the following search terms; proton-pump inhibitors, kidney injury, renal diseases, adverse events of proton-pump inhibitors, acute interstitial nephritis, renal injury and chronic kidney disease. The PPIs are known as one group of drugs that are well tolerated in healthy subjects and where serious harms are rare. The some reports reveal that long-term administration of PPIs is associated with adverse effects such as: increasing the incident risk of kidney injury, hyper-secretion of gastric acid after their withdrawal, bone fracture, decreased levels of blood magnesium, interaction with metabolism of antiplatelet agents, increased risk of enteric infections and community-acquired pneumonia.

Implication for health policy/practice/research/medical education:
This paper aimed to review the impact of proton pump inhibitors (PPIs) on kidney function and structure by presenting the updated information in this regard. The adverse effects associated with the administration of PPIs include an increase in the incident risk of kidney injury, hyper-secretion of gastric acid after their withdrawal, bone fracture, decreased levels of blood magnesium, interaction with metabolism of antiplatelet agents, increased risk of enteric infections and community-acquired pneumonia.

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Introduction

Proton pump inhibitors (PPIs) are one group of drugs that inhibit gastric acid secretion by binding irreversibly to the gastric proton pump. They include several different agents, such as omeprazole, pantoprazole, lansoprazole, deslansoprazole, etc. They are used in treatment of conditions such as duodenal and gastric ulcer, Zollinger-Ellison syndrome, gastro-esophageal reflux disease, Barrett's esophagus and *Helicobacter pylori* infection of the upper gastro-intestinal tract. They are firstly introduced in the late 1980s (1). According to the U.S. Food and Drug Administration (FDA), about 21 million people have consumed one prescription of PPIs in the United States in 2009 (2). All PPIs possess a common mechanism of action for reducing parietal cell acid production by blocking gastric hydrogen potassium ATPase (1).

The PPIs are known as one group of drugs that are well-tolerated in healthy subjects and where serious harms are rare (2). In fact, the exposure to PPIs for kidney injury is not established yet, but there are several evidences that adumbrate on PPIs administration. The recent reports show an association between long-term prescription of PPIs and the appearance of adverse effects, for example; hyper-secretion of gastric acid after their withdrawal (3), with bone fracture (4) and low levels of magnesium in blood (5). Also, reducing the benefits of anti-platelet agents such as clopidogrel in patients with acute coronary syndromes, is followed by the inhibition of hepatic

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enzymes, which account for the metabolism of antiplatelet agents (6). PPIs have also been linked to increased risk of enteric infections such as clostridium difficile-associated diarrhea (7) and community-acquired pneumonia (8).
On the other hand, according to a case-control over the 10-year period, the peptic ulcer disease incidence was about 10–12 times higher in patients with chronic kidney disease (CKD) than in those without CKD especially in elderly CKD patients (9). In addition, it was pointed out that, some factors such as hemodialysis therapy and administration of ulcerogenic medications (nonsteroidal anti-inflammatory drugs, aspirin and clopidogrel) may further increase peptic ulcer risk in CKD patients (6,9). Hence, CKD is a strong risk factor for peptic ulcer disease(10).
Recently much attention has been directed to consider the probable association between exposure to PPIs and an increase in the incidence of kidney injury (10).
This paper aimed to review the impact of PPIs on kidney function and structure by presenting the updated information in this regard.

Materials and Methods

For this review, we searched in electronic databases including Google Scholar, EMBASE, MEDLINE, Scopus and EBSCO during the period of 1980 to 2017 by using the following search terms; proton-pump inhibitors, kidney injury, renal diseases, adverse events of proton-pump inhibitors, acute interstitial nephritis, renal injury and chronic kidney disease. We used review articles, clinical trials, cohort studies, case-control studies and case reports that were relevant to our topic.

Potential risk of kidney injury after administration of PPIs

Acute interstitial nephritis (AIN) is an important form of nephritis changing the interstitium of the kidneys around the tubules resulting in acute renal failure from immune-mediated tubulointerstitial injury (9,10). Drugs commonly induce AIN thought an idiosyncratic and cell-mediated immunologic reaction (10). Some case reports suggest that AIN, which is induced by PPIs, eventually leads to acute renal failure. The patients who presented weight loss, nausea, vomiting and a rise in serum creatinine concentration after the administration of PPIs, were diagnosed by renal biopsy (11,12).
According to a case serious study, PPIs were a common identified cause of AIN in the Auckland area where even incomplete recovery occurred after withdrawal of the drug. Elevated erythrocyte sedimentation rate and C-reactive protein may be an alarm for clinicians on the onset of renal failure (12).
A case control study showed that the incidence of renal disease was two times more in patients using PPIs compared to those who did not use PIPs. This quasi-experimental design supported an association between renal injury with PPIs exposure which imply considering and controlling of different aspects of kidney disease following PPI administration (13).
In a cohort study, Antoniou et al compared the risk of acute kidney injury and AIN in older patients taking PPIs with patients not using these drugs. They found a raised risk of AKI due to AIN following PPI administration in older individuals (14).
Chronic kidney disease is a process of worsening the kidney function over months or years without specific symptoms (9). It can associate with an increased risk of death and cardiovascular events. The risk factors of chronic kidney disease are not fully described yet. However, diabetes mellitus, hypertension and some medications can be potential factors to increase the prevalence of chronic kidney disease. Recently, a cohort study explained the association between PPI exposure and the increase of incident kidney disease in general population which leads to the idea that PPI administration is an independent risk factor for chronic kidney disease in addition to AKI (15).
More recently, a systematic review showed that, interstitial nephritis is responsible for approximately 15% of acute renal failure cases after PPI exposure with the mean duration about 13 weeks in the absence of baseline renal failure. They detected nephritis following measurement of serum creatinine and conducting renal biopsy. All patients recovered in an average time of 35.5 weeks. Only one case needed to permanent dialysis. There were no reports of death (16).
The effects of PPIs are dependent on the transport of protons. They inhibit acid secretion by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system of the gastric parietal cells (1). Vacuolar protons adenosine triphosphatase are multi-subunit complexes that mediate the adenosine triphosphate-dependent transport of protons. They are located in the kidney medulla and osteoclast-containing medullary bone that may be inhibited by PPIs (1,11).
Overall, the association of acute kidney injury and this group of drugs may be overstated by considering the low risk of recurrence. However, kidney injury should be considered as a high index of suspicion in renal failure patients taking PPIs.

Potential risk of hypomagnesemia by PPIs

Magnesium homeostasis is usually related to intestinal absorption, renal excretion and exchanging with bone. Hypomagnesemia is usually associated with hypocalcemia, hypokalemia and hypoparathyroidism. The first report was in 2006, regarding two hypomagnesemia cases associated with the administration of proton-pump inhibitors which were presented with carpopedal spasm due to severe hypomagnesemia and hypocalcemia accompanied with lacking appropriate rise in serum levels of parathyroid hormone (15).
The prevalence of PPI-induced hypomagnesaemia is not exactly known. In fact, they represented the tip of an iceberg in patients with hypomagnesaemia related to PPI administration. A systematic review and meta-analysis study showed that PPI therapy for one year or more

can lead to severe and symptomatic hypomagnesemia particularly in patients ranged between 50 and 80 years (5). In addition, this type of hypomagnesemia often occurred with low or normal parathyroid hormone levels, calcium levels in blood of <2.20 mmol/L and blood potassium level below 3.50 mmol/L. As regards, there was not an association between the proportion of hypomagnesemia with the degree of hypokalemia or hypocalcemia. Sometimes, it was seen in accompaniment thiazide or loop diuretic administration, alcohol abuse, poor renal function or small bowel resection. However, it was resolved when PPI therapy was withdrawn but recurred when PPI administration was started again even with another PPI (5). In contrast, Markovits et al did not find any association between magnesium levels and histamine type-2 receptor antagonists (17).

Hypomagnesemia associated-PPI administration may lead to severe symptoms such as tetany, seizures, convulsions, cardiac arrhythmia. The molecular, physiological factors, risk factors and mechanisms that may be involved in the association between hypomagnesemia and PPI are not exactly understood (17). There are some hypotheses that PPI administration may reduce the intestinal absorption of magnesium throughout an effect on tight junction function directly of gatekeeper of transepithelial magnesium ion transport-transient receptor potential Melastatin 6 (TRPM6) or as a result of intestinal pH changes (18). A study suggested that genetic factors might increase susceptibility to PPI-induced hypomagnesemia in patients with TRPM6 mutations (19).

However, hypomagnesaemia symptoms are non-specific or may be misinterpreted. Also measurements of serum magnesium are not checked as a routine biochemical profile. So, it is better that indications for continuing PPI therapy in patients are kept under regular review, for example patients on non-steroidal anti-inflammatory drugs. Nevertheless, if PPI therapy is necessitated for long time, the serum magnesium should be measured regularly at least in patients with symptoms or signs of magnesium deficiency, concurrently use other decrescent agents for magnesium level or poor renal function. When hypomagnesemia secondary to PPI therapy is recognized, the PPI then switches to a histamine type-2 receptor antagonist. Prescription of magnesium supplements may be helpful.

Potential risk of infections

There are several reports concerning the potential risk of critical infections among individuals treated with PPI agents. In PPI users, enteric infections such as clostridium difficile colitis (7,20) and pulmonary infection (8) could be particularly frequent. The mechanisms underlying predisposition of infections associated to PPI exposure are not exactly clear (1). Gastric acid that is secreted by the parietal cells in the stomach, has an important role in the inhibition of ingested organisms and bacterial pathogens (7). PPIs agents can impair overthrow of ingested microorganisms due to selectively suppression gastric acid. On the other hand, researchers have pointed to potential drug-induced disorders on the bactericidal capacity of leukocytes (3).

Clostridium difficile is the main infectious agent which leads to antibiotic associated-diarrhea and hospital-acquired infections. The several published articles have shown an increased risk of clostridium difficile infection with different durations of PPI therapy as well as enteric infections with *Shigella*, *Salmonella*, campylobacter and listeria in hospitalized patients (7). In addition, an increased risk of clostridium difficile infection in non-hospitalized patients on PPIs therapy occurs. Recently, a multi-country study, confirmed the association between PPI exposure and clostridium difficile infections across Australia, Korea, Taiwan, Japan and Canada (20).

Overall, PPI therapy within a short course may be useful in selected patients. Accordingly, it should be discontinued in asymptomatic patients or in patients having the risk factors on gut flora. It is better that patients on PPIs be aware on infection susceptibility particularly on bacterial diarrhea. They should also learn to exercise care on intake of higher risk diets such as raw and unpasteurized foods especially during living in tropical area or traveling to tropical regions of the developing world. Even it may be considered to the administration of chemoprophylaxis drugs to prevent this illness in PPI users.

A systematic review demonstrated a 1.5-time increased risk of community acquired pneumonia with outpatient PPI therapy plus a 1.6-fold increased risk for hospitalization with community acquired pneumonia (8). While PPI administration may cause community acquired pneumonia both through acute pH dysregulation as well as altering respiratory flora and micro-aspiration of the change of the gut flora (8). However, the pathophysiologic mechanisms of association between community acquired pneumonia and PPI exposure is not clarify known and it is necessary to conduct further studies. It is better to consider risks and benefits before prescription of PPIs and increase knowledge on this risk factor for adults presenting with pneumonia.

Potential risk of other adverse events

There are some reports that PPIs may interact with anti-platelet agents in patients with acute coronary syndrome (6). The mechanism of this effect is unknown. In fact, PPIs can inhibit the hepatic enzyme (CYP2C19) which is needed for activation of clopidogrel (21). Dimethylarginine dimethylaminohydrolase is an enzyme that is found in all mammalian cells. It degrades methylarginines, specifically asymmetric dimethylarginine and NG-monomethyl-L-arginine. Asymmetric dimethylarginine is an endogenous inhibitor of nitric oxide synthase. Plasma levels of asymmetric dimethylarginine are correlated with increased risk for cardiovascular disease, likely owing to its attenuation of the vasoprotective effects of endothelial nitric oxide synthase. PPIs also inhibit the activity of dimethylarginine dimethylamino hydrolase that metabolizes asymmetric dimethylarginine then

competitive inhibitor of endothelial nitric oxide synthase (3,6,10). The proses lead to raise the risk of vascular inflammation and thrombosis due to increase oxidative stress (6).

There are not clear guidelines for PPIs prescription in patients under treatment with antiplatelet agents particularly newer agents. But it is necessary to more clinician's attention and aware on especial conditions such as acute coronary syndrome or cerebrovascular accident and also to evaluate as an individual basis about risks and benefits of concomitant therapy with antiplatelet agents and PPIs.

Several studies have showed an increased risk in hip, spine, wrist and other site fractures especially in patients who have taken PPIs for longer than one year duration (4). The electrolyte disturbance and vitamin deficiency were aggravating factors for this adverse events. PPIs inhibit intra-gastric secretion of hydrochloric acid that facilitates calcium absorption thought small intestinal. On the other hand, osteoclasts have proton pumps, therefore PPIs can potentially directly effect on calcium absorption thought small intestinal and reducing bone resorption of calcium (4,22). Malabsorption of vitamin B_{12} (cobalamin) and other nutrient elements were observed in the patients with atrophic gastritis or achlorhydria (22). It may be happened due to diminution in upper small intestine gastric acid, bacterial overgrowth and increase bacterial consumption of cobalamin. It is possible that, PPIs exposure influence the malabsorption of vitamin B_{12} but is not prove yet. Hence, assessment for vitamin B_{12} deficiency in patients on PPI therapy is seldom recommended (23). In addition, iron absorption related to gastric acid secretion was been detected. Infect, long term PPI therapy may cause iron malabsorption due to the risk of achlorhydria and gastric acid hypo-secretion, although this matter did not demonstrate significant yet (23). There is not approval to monitor patients on PPI therapy for iron deficiency anemia.

While there is not sufficient evidence to be certain on a causal relationship these adverse effects with PPIs administration, however, it needs to level elevation of clinical suspicion. Furthermore, clinicians should be aware on risk factors some such as age of patients, frail individuals and malnourishment particularly in chronically hospitalized patients to assess benefits of therapy against risks. Large randomized and prospective trials may also show or establish direct cause and effect associations between PPIs and adverse events.

Conclusion

Although, PPI agents have improvements in treatment of upper GI tract disorders, they are not without risk of adverse effects. The results of this review support the association between PPI use and renal disease and kidney injury, which are important implications for public health. These adverse effects may not be easily attributed to the treatment of PPIs and are often reverse and rarely life-threatening. Hence, it is necessary that the awareness of physicians and pharmacists is increased to the recognition of the patient's complaints and the clinical manifestations of these potentially harmful events, particularly in the first weeks after the initiation of the treatment by PPIs. In fact, more prescriptions of PPIs should not be clinically indicated, hence clinicians should monitor patients and stop the indiscriminate use of these drugs. In addition, it is necessary that more research is conducted on the underlying mechanisms of this association.

Furthermore, non-pharmacological proceedings such as attentive observation, life style modification (for example weight reduction, stress reduction, eating smaller meals well before sleep and smoking cessation) may be useful and substitute in dyspepsia resolve.

Authors' contribution

LM and MH searched and gathered the related articles. MH prepared the draft. LM edited the final manuscript. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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