

Impact of proton pump inhibitors on renal function and structure; new concepts

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Abstract

Proton pump inhibitors (PPIs) such as omeprazole, pantoprazole, esomeprazole and lansoprazole are the most popular therapies for reflux disease and heartburn. Applications of PPIs are commonly safe and well-accepted by physicians, with an adverse effect occurring at a rate of about three percent. The common side effects are dizziness, constipation, headaches, diarrhea and cutaneous responses. PPIs can influence in all cells of body that are related to deadly diseases such as heart attacks, kidney disease and dementia. Some research studies have found that PPIs were related to an inflammatory process in the kidneys as acute interstitial nephritis. This review will emphasis on conducted researches about adverse effects of PPIs on the kidney.

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Introduction

Proton pump inhibitors (PPIs) include a class of drugs widely used for acid peptic disease treatment. They have known as one of the most important treatment developments in the gastroenterology field during recent 15 years (1). In fact, they are the third highest-selling medication in the United States; it means that about 15 million Americans pay \$10 billion for such drugs every year (2). Since their finding in the late 1980s, PPIs, like omeprazole, lansoprazole and pantoprazole (1-3), have been largely consumed for the therapy of acid-related disorders (3). Different types of PPIs structures are shown in Figure 1.

It has been accepted that the mechanism of action of the PPIs include the inhibition of the H⁺/K⁺-ATPase in gastric mucosal parietal cells (4). This enzyme is accountable for the secretion of hydrogen ions (H⁺) in exchange for potassium (K⁺) in the gastric lumen, and its inhibition could reduce gastric acidity (5). Their efficiency is superior to histamine-2 receptor antagonists and they are used to apply for the therapy of gastroesophageal reflux disease (GERD) (6), peptic ulcer inhibition in patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) (7) and *Helicobacter pylori* eradication procedures (8). Similarly, PPIs are often consumed for the inhibition of stress ulcer (9).

Moreover, PPIs are mostly well accepted,

Core tip

Proton pump inhibitors (PPIs) are extensively recommended as the best treatment for acid-related gastrointestinal diseases; nevertheless, the safety of long-term PPIs administration still need serious prospective examination.

because the frequency of adverse effects related with PPIs is similar to the placebo, with a total incidence under 5% (1-3). In other words, the variety and the frequency of adverse effects are similar to those detected with histamine H₂-receptor blockers, with most common side effects of nausea, diarrhea, headache and abdominal pain. Except for diarrhea, the side effects of PPIs do not seem to be associated with dosage, age or period of therapy (3,10). Indeed, diarrhea appears to be attentive to the profound acid inhibition that occurs to change the bacterial content of the gut. As stated earlier, the overall occurrence of diarrhea is less than 5%, which makes this effect likely to be both age- and dosage-related (10,11).

As a matter of fact, short-term safety of the oldest agents, lansoprazole and omeprazole (<12 weeks of therapy) has been well-diagnosed (12). Likewise, the safety reports of newer agents like pantoprazole and rabeprazole seem to look like the reports of the older agents (11,12). Despite the fact that this is true, health care providers are



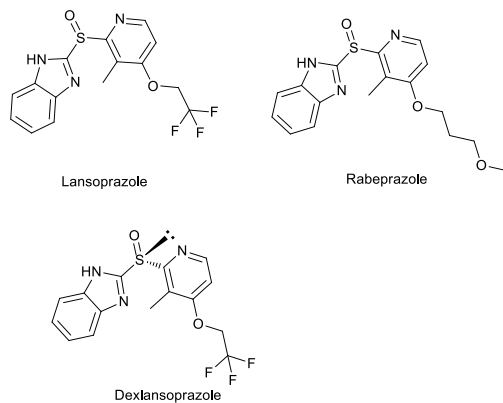


Figure 1. Structural formula of the proton pump inhibitors (PPIs); lansoprazole, rabeprazole and dexlansoprazole

progressively prescribing PPIs for long-time, sometimes for lifetime use, often in the absence of suitable indications, and there is rising concern for probable adverse effects from such long-time treatment. Besides, since many PPIs are accessible everywhere, many patients may consume them autonomously and for long periods of time without seeking medicinal care (13).

Renal complications sometimes may cause some problems during drug treatment and it is of great importance that clinicians could identify them (14). Hypomagnesemia, drug–drug interactions and hyponatremia from gastrointestinal damages could occur with PPIs, but acute interstitial nephritis is the most generally detected adverse effect on the kidney (15). In addition, current data suggest that chronic kidney disease (CKD) may be an essential problem resulting from these agents (14).

This review will revise researches conducted on PPIs effects on the kidney, specifically omeprazole and pantoprazole.

Materials and Methods

In this review a variety of sources have been used by searching through PubMed/Medline, Scopus, EMBASE, Google Scholar, EBSCO and directory of open access journals (DOAJ). The search was conducted using combination of the following keywords or their equivalents; include; PPIs, kidney, acute interstitial nephritis, adverse event, side effect, omeprazole, pantoprazole, esomeprazole and lansoprazole. It is used of original article, review articles, clinical trials, cohort studies and case-control studies that were relevant to our topic.

Acute interstitial nephritis

Acute interstitial nephritis is a cell-mediated and humoral sensitivity reaction that results in the inflammation of renal tubules and interstitial area which could lead to acute renal failure (14). In addition, research suggests that acute interstitial nephritis accounts for 6%–8% of the cases with acute renal failure (16). Acute interstitial nephritis is mostly identified in renal failure with inactive urinary sediment (proteinuria and hematuria); in this situation, it may occur in 27% of patients (16).

Furthermore, drugs containing NSAIDs, anti-biotics,

PPIs and diuretics may account for 60% of cases with acute interstitial nephritis (AIN) (17). Although all PPIs have been reported to have a relation with AIN, but it is mostly referred to omeprazole (16). Additionally, PPIs-related AIN is rare, distinctive and subsequently difficult to forecast (16). In fact, AIN is a fairly uncommon reason for acute kidney injury (AKI), accounting for just 2%–3% of all renal biopsies (18). In spite of this, in people with AKI and normal appearing kidneys on ultrasound, AIN is a much more common reason, accounting for up to 27% of biopsy- proven instances (18).

The most important limitation of the above-mentioned literature is the basis of data, limited to observational data that did not sufficiently control for confounding elements. The mainstay of treatment for drug-induced AIN is timely diagnosis, recognition and discontinuation of the causative factor (17).

Moreover, AINs relation with PPIs, in this case omeprazole, was first published in 1992. In this case, a 74-year-old woman who had taken omeprazole for 6 months with increased fatigue, malaise, was noted to have proteinuria, eosinophiluria and hematuria (19). Likewise, after 12 years, 29 more cases with omeprazole were introduced, 23 of them were biopsy- demonstrated (20,21). In 2004, Torpey and colleagues described that other PPIs including pantoprazole and lansoprazole were also implicated in two other great instance series (22).

Furthermore, PPIs-related interstitial nephritis is infrequent, characteristic and difficult to forecast. In other words, it needs a high level of medical suspicion. While there is no enough evidence to create a causal relationship with confidence, there might be a low-prevalence connection (23). Hence, it is better that identification of PPIs-induced AIN is made according to renal biopsy assumed the infrequency of classic marks and symptoms. Geevasinga and colleagues reported the largest information to date by Australian researchers in 2006; i.e., retrospective information collection from two training clinics (more than 10 years). They pointed to 88% of the people under tested that not all of them appeared to have eosinophil in the tubulointerstitium. Similarly, glomeruli were regular in most cases, if there was also another unconnected kidney injury present (24).

Likewise, the pathophysiology of medication-induced AIN has largely been inferred from animal examples of immune-mediated trial about AIN (25). These examples could suggest that the medication or one of its metabolites may either operate as a planted antigen, operating as a hapten, imitate a renal antigen or accumulate in the interstitial area as a distributing immune complex (25). Moreover, an in-depth conversation of the pathogenesis of medication-induced AIN has also been studied (25). To our information, the pathogenesis of omeprazole-induced AIN has not been clarified. However, Montseny and colleagues explained an interesting relationship between omeprazole-induced AIN and people with immunologic derangements (26). Some other scientists also detected that omeprazole-induced AIN had occurred in several

persons with underlying immunologic anomalies such as sarcoidosis, ocular myasthenia, activist immunoglobulin G perinuclear antineutrophil cytoplasmic antibody and Sjögren's syndrome (26,27).

In fact, the timing from beginning of drug to exhibition with kidney involvement seems to be quite variable, happening from 1 week to 9 months (20). Combining all evidences such as signs and/or identification of AIN may lead to the fact that it can happen on average 9.9 weeks after the beginning of PPIs treatment (not very distant from the time frame or 11 weeks designated by Geevasinga and colleagues) (20). In patients who restart the medication after suspected PPIs-induced AIN, signs have occurred much more rapidly (i.e. commonly advancing kidney injury within days) (27).

Although this information is not enough for demonstration of reason and effect, but there might be some concern for AIN's high frequency with PPIs treatment. Anyhow, management of AIN related with PPIs is similar to that of other types of drug-induced AIN (16,17).

Omeprazole effect on kidney

Omeprazole (Figure 2), with different names like "Prilosec" and "Losec", is a proton-pump suppressor that is prescribed extensively for therapy of acid-peptic disorders (1). It was advertised in the late 1980s for the first time. There are different types of treatment; for example, short-time therapy is usually used in the therapy including peptic ulcer disease, *H. pylori* eradication (5), maintenance treatment as an aid in the management of gastroesophageal reflux disorders (6) and prophylaxis against ulceration because of nonsteroidal anti-inflammatory medications (7). Omeprazole is usually well-accepted by both patients and physicians due to having a useful effect profile alike histamine-2 blockers (28). Similarly, usual side effects may be nausea, increased intestinal gas, headaches and vomiting (28). In addition, other reported serious adverse effects may include *Clostridium difficile* colitis, an increased chance of bone fractures, an increased chance of pneumonia, the capacity of masking stomach cancer, hepatic and renal failure (1,3,28).

Interstitial nephritis is an infrequent side effect that has been related with omeprazole (27). The first reported instance of AIN related to omeprazole was shown by Ruffenach and colleagues in 1992 (19). Based on described studies in literature; AIN was identified later after an average of 2.7 months initiating treatment with 20 to 40 mg of omeprazole daily (29).

In general, AIN is a serious but remediable side effect of omeprazole treatment. Physicians should be alert of

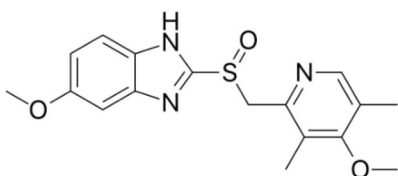


Figure 2. Structural formula of omeprazole.

this disorder and examine it in any patient who is taking omeprazole and has a great chance of growing renal dysfunction. Management contains of immediate removal of omeprazole, supportive treatment and continuation of hemodialysis if necessary.

Pantoprazole effect on kidney

Pantoprazole (Figure 3), is famous as "Protonix", has its special place in the class of PPIs that can covalently restrain hydrogen-potassium-adenosine triphosphatase in gastric parietal cells. This group of medications is more effective than histamine H₂-receptor antagonists in decreasing gastric acid excretion and acid-related disorders therapy (1).

A number of common side effects of pantoprazole occurring in adults may include diarrhea, headache, abdominal pain, nausea, flatulence, vomiting, dizziness and joint pain (>2%) (30). In other words, consumption of pantoprazole for a prolonged period, may cause chronic inflammation of atrophic gastritis or stomach lining, low magnesium and vitamin B12 deficiency (31).

In 2003, the first case of AIN caused by pantoprazole was reported by Ra and Tobe (32). Reported cases of AIN due to pantoprazole is less than omeprazole. Although, both omeprazole and pantoprazole are metabolized significantly through the hepatic CYP2C19 isoenzyme and, to a minor extent, CYP3A (33). These benzimidazole derivatives are chemically related and their key metabolites are structurally alike as well. The different pharmacodynamics attributes of these medications might offer a pronouncement. In fact, PPIs are prodrugs that are activated in an acid milieu (32). Yet, pantoprazole has a more PH choice than omeprazole and is stable under neutralized to mildly acidic milieus in vitro. Also, it could especially bind in vitro to the active areas of the proton pump, everywhere omeprazole has extra positions of binding. Likewise, another reason for the minor number of reports of pantoprazole is its newer position on the market compared to omeprazole (32).

Furthermore, physicians should be informed that medication-induced AIN may be able to interact with PPIs (i.e. pantoprazole) more than omeprazole.

Discussion

PPIs are very effective medications that are largely used worldwide. In the past years, there has been a concern about their over-utilization and recommendation in unnecessary conditions, for instance GERD (3).

PPIs, substituted benzimidazoles, were presented firstly in the late 1980s, as a controller of gastric acid and were chosen top of histamine H₂-receptor blockers (1,33). Furthermore, PPIs are commonly administered as capsules or enteric-

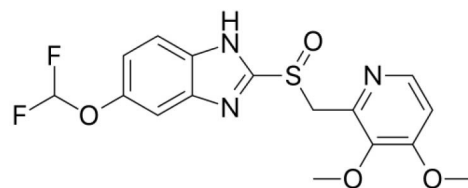


Figure 3. Structural formula of pantoprazole.

coated tablets, which could pass through the stomach intact and absorbed in the proximal small intestine (1, 33). After absorption, all PPIs possibly have a moderately short plasma half-life (about one to two hours) (1,33). In fact, their time of action is much longer than H₂-receptor blockers due to their unique procedure of action (4). They are lipophilic weak bases which can transfer the parietal cell membrane and come in the acidic parietal cell duct. In this acidic situation, it becomes protonated, creating the activated sulphenamide (RS(O)₂NR'₂) structure of the medication that binds covalently with the H⁺/K⁺ ATPase enzyme that could lead to irreversible reserve of acid discharge by the proton pump (12). At that situation, the parietal cells must create new proton pumps or activate resting pumps to reoccupy its acid discharge (12).

Furthermore, PPIs are absorbed through the CYP450 system. In addition, metabolism of active medication may occur primarily through CYP2C19 and CYP3A4 into passive metabolites (12,33), but there are dissimilarities among the drugs with rabeprazole due to a non-enzymatic metabolic path (34). Inactive pieces of metabolized medication are defecated in the urine, while just 0%–1% of active medication is recovered in the urine (1). Consequently, no dosage change is required in persons with underlying CKD, AKI or end-stage renal disease on chronic dialysis.

Moreover, PPIs have enabled better therapy of diverse acid-peptic disorders, including gastroesophageal reflux disease, nonsteroidal anti-inflammatory medication-induced gastropathy and peptic ulcer disease (4-7). Similarly, PPIs have minimum side effects and few significant medication interactions, and they are usually considered safe for long-term therapy (4). Despite this, PPIs are just contraindicated if the person has a known history of sensitivity to them, and they should be consumed with caution in persons with severe hepatic disorders (12).

However, PPIs-induced AIN must be doubted as a potential make of AKI in persons devoid of an else evident cause of kidney dysfunction. Above all, despite the improvement of the kidney function, in more than half of the cases following medication withdrawal, most patients are left with some level of CKD (35).

Even so, PPIs seem very effective medications with a good safety profile. Yet, some studies suggest that they may create kidney injury, since they are often overused and recommended without a certain acid associated sign. In order to minimize the incidence of their infrequent side effects, and decrease the medical costs, there should be paid attention to their administration specifically long-term treatments (3).

Conclusion

This review has revealed that PPIs are extensively recommended as the best treatment for acid-related gastrointestinal diseases; nevertheless, the safety of long-term PPIs administration still need serious prospective examination.

Authors' contribution

AA searched and gathered the related articles as well as writing. MA prepared the draft. MH edited the final manuscript several times. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

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

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