Long -Term Kidney Outcomes among Users of Proton Pump Inhibitors

Thesis

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List of Abbreviations

Abb.	Full term
AEs	*Adverse Events*
AIGO	*Associazione Italiana dei Gastroenterologi Ospedalieri*
AIN	*Acute Interstitial Nephritis*
AKI	*Acute Kidney Injury*
ATPase	*Denosine Triphosphatase*
CAP	*Community-Acquired Pneumonia*
CKD	*Chronic Kidney Disease*
DRESS	*Drug Reaction with Eosinophilia and Systemic Symptoms*
eGFR	*Stimated Glomerular Filtration Rate*
EoE	*Eosinophilic Esophagitis*
ESRD	*End-stage Renal Disease*
FD	*Functional dyspepsia*
FIMMG	*ederazione Italiana dei Medici di Medicina Generale*
GERD	*Gastroesophageal Reflux Disease*
GI	*Gastrointestinal*
GIB	*Gastrointestinal Bleeding*
H2RAs	*Histamine2-receptor Antagonists*
HR	*Hazard Ratio*
MEN-1	*Multiple Endocrine Neoplasia-1*
MI	*Myocardial Infarction*
NSAIDs	*On-steroidal Anti-Inflammatory Drugs*

List of Abbreviations (Cont...)

Abb.	Full term
OR	*Odds Ratio*
OTC	*Over- The- Counter*
PAC	*PPI + amoxicillin + clarithromycin*
PACAP	*Ituitary Adenlase Cyclase-Activating Peptide*
PAL	*PPI + amoxicillin + levofloxacin*
PAM	*PPI + amoxicillin +metronidazole*
PAMC	*PPI + Amoxicillin+ metronidazole+ clarithromycin*
PBMT	*PPI + bismuth+ metronidazole+ tetracycline*
PMC	*PPI + metronidazole+ clarithromycin*
PPIs	*Proton Pump Inhibitors*
RCT	*Random Controlled Trials*
RE	*Reflux Esophagitis*
SGU	*Stress Gastric Ulcers*
SIF	*ocietà Italiana di Farmacologia*
ZES	*Zollinger-Ellison Syndrome*

ABSTRACT

Our study revealed that Long- term use of PPIs (40 mg of omeprazole for 6 months) can be safe among healthy objects without previous renal diseases or chronic diseases affecting the kidneys; and not using poly medications, however, this study is lacking the time needed and the appropriate sample size in order to generalize that hypothesis.

Careful consideration by the prescriber of appropriate indication, patient cofactors, and the expected dose and duration of treatment is a necessary part of responsible use of any drug, including PPIs.

Keywords: Proton Pump Inhibitors - Random Controlled Trials - Drug Reaction with Eosinophilia and Systemic Symptoms

INTRODUCTION

Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have become the mainstay in treatment of acid-related disorders. When compared.with earlier agents such as histamine2-receptor antagonists (H2RAs), synthetic prostaglandin analogs, and anticholinergics, PPIs have demonstrated consistent reliable tolerance, excellent safety, and generally superior acid suppressing capability than previous agents ***(Farley et al., 2000)***

Additionally, over- the- counter (OTC) have been available for more than 10 years and are indicated.for short term use in managing heart burn experienced patients at least twice weekly ***(Vakil et al., 2006)***

Despite comprehensive clinical evidence of the benefits using PPIs to treat acid-related disorders, novel observational studies linking PPIs and adverse events (AEs) including: osteoporosis, acute interstitial nephritis (AIN), chronic kidney disease, myocardial infarction (MI) and dementia have resulted in greater scrutiny, leading some clinicians and patients. to discontinue treatment ***(Zhoub et al., 2016)***

The secretion of gastric acid is a complicated and continuous process associating neuronal, paracrine and endocrine pathways. These separate signaling mechanisms converge at a common endpoint to enhance the secretion of hydrogen ions by gastric parietal cells.

Since proton pump inhibitors (PPIs) block acid secretion from all three pathways simultaneously, they are considered the most potent medications available to lower. gastric acid secretion ***(Wallace et al., 2011).***

Proton pumps are present on the plasma membrane of gastric parietal cells. They create an acidic environment in the gastric lumen by exchanging one hydrogen ion for one potassium ion via the H^+/K^+-ATPase pump. All PPIs are substituted benzimidazole derivatives that irreversibly inhibit the proton pump. Upon protonation to the active sulfonamide in the acidic.secretory canaliculus, the drug covalently binds to the sulfhydryl group on the proton pump to prohibit acid secretion into the gastric lumen. Acid secretion will resume only after a new proton pump is synthesized, about 24–48 h. PPIs are excreted primarily via hepatic metabolism by cytochrome 2C19 and 3A4; renal excretion is negligible. ***(Barkun et al., 2009)***

There are currently six PPIs available for use: omeprazole (Prilosec®, AstraZeneca, London, UK), lansoprazole (Prevacid®, Takeda Pharmaceuticals, Tokyo, Japan), pantoprazole (Protonix®, Wyeth Pharmaceuticals, NJ, USA), .esomeprazole (Nexium®, AstraZeneca, London, UK), rabeprazole (AcipHex®, Eisai, Tokyo, Japan) and dexlansoprazole (Dexilant®, Takeda Pharmaceuticals) ***(Wilhelm et al., 2013).***

Regarding the kidneys, Proton pump inhibitor (PPI) use is associated with an increased risk of acute kidney injury (AKI), incident chronic kidney disease (CKD), and.progression to end-stage renal disease (ESRD). PPI-associated CKD is assumed to be mediated by intervening AKI. However, whether PPI use is associated with an increased risk of chronic renal outcomes in the absence of intervening AKI is.unknown ***(Xie et al., 2016).***

The biological mechanisms supporting the observed association of PPI with chronic renal outcomes are unevident. Poesen etal proposed a hypothesis that in.addition to AKI, altered gut microbial composition and metabolism may be in the causal pathway between PPIs and CKD ***(Poesen et al., 2016).***

Experimental evidence in rats suggests that PPI intake limits the regenerative.capacity of the liver after partial hepatectomy ***(Kucuk et al., 2006).***

It is unclear whether PPI exposure also limits the regenerative capacity of renal tubular cells, for example. Such a mechanism, if verified, may at least partially explain the increased risk of renal outcomes in PPI users. It has also been observed that administration of PPIs upregulates the expression of mRNA and protein level and subsequent increased activity of the heme.oxygenase-1 enzyme in gastric and endothelial cells ***(Poesen et al., 2016)***.

Heme oxygenase-1 is generally seen as salutatory in the setting of AKI as it may reduce the sensitivity of the kidney to AKI and may reduce the propensity.of AKI to CKD transition. However, the salutary properties of heme oxygenase-1 are clear at lower doses and are vitiated at higher doses or in cases of sustained duration of expression ***(Nath et al., 2014).***

AIM OF THE WORK

The aim of this work to define the effect of the long term use of PPIs on the kidneys in terms of assessing various kidney functions including serum creatinine, urea, BUN, estimated Glomerular filtration rate (eGFR), serum potassium and calcium levels.

Chapter 1
PROTON PUMP INHIBITORS

PPIs- Review of literature

In the 1960s, both physicians and surgeons managed peptic ulcer disease. Medical therapy was almost unsatisfactory, the available medications being. poorly efficient. When it failed, or when an ulcer bled or perforated, surgical intervention was often required. The techniques used included partial gastrectomy with anastomosis to the duodenum (Billroth I), gastrectomy with gastrojejunostomy (Billroth II), Roux-en-Y bypass, and highly-selective vagotomy with or without pyloroplasty. The results were often good, but at the cost of undesired effects, including dumping syndrome, stomal ulceration, gastrojejunocolic fistulae, and a risk of cancer in the gastric stump ***(Gorey et al., 1984).***

However, in the 1970s more efficient medications and new therapeutic approaches started to emerge. For example, high doses of antacids, .apart from providing symptomatic relief, could be curative. The same recurrence rates were observed after the end of therapy with both antacids and histamine H2 receptor antagonists and long-term therapy with either treatment maintained healing equally -well ***(Miller et al., 1990).***

Nowadays, surgery is still sometimes performed, however, peptic ulceration and its complications are largely managed by physicians, whether by endoscopic or pharmacological means. Fiber-optic endoscopy came of age in the 1970s. And elucidation of the physiology of gastric acid secretion led to the development of medications that reduce gastric acid secretion such as anticholinergic drugs selective for muscarinic M1receptors (pirenzepine), histamine H2 receptor antagonists., and prostaglandins, the last uniqueally used in peptic ulceration in patients. Taking non-steroidal anti-inflammatory drugs (NSAIDs) ***(Schubert et al., 2011).***

The H+/K+-adenosine triphosphatase (the proton pump) in the apical surfaces of gastric parietal cells is the final common pathway for.medications with different mechanisms of action that alter gastric acid secretion. This observation led to the development of a range of.substituted benzimidazoles that inhibit the pump, that have come to be known as proton pump inhibitors (PPIs), of that omeprazole was the first to be.developed for clinical use. Lately, newer reversible PPI inhibitors, potassium-competitive acid blockers such as vonoprazan, have also become available ***(Hori et al., 2010).***