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REVIEW ON PROTON PUMP INHIBITOR

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Abstract: Proton pump inhibitors (PPIs) were clinically introduced more than 25 years ago and have since proven to be invaluable, safe, and effective agents for the management of a variety of acid-related disorders. Although all members in this class act in a similar fashion, inhibiting active parietal cell acid secretion, there are slight differences among PPIs relating to their pharmacokinetic properties, metabolism, and Food and Drug Administration (FDA)-approved clinical indications. Nevertheless, each is effective in managing gastroesophageal reflux disease and uncomplicated or complicated peptic ulcer disease. Despite their overall efficacy, PPIs do have some limitations related to their short plasma half-lives and requirement for meal-associated dosing, which can lead to breakthrough symptoms in some individuals, especially at night. Longer-acting PPIs and technology to prolong conventional PPI activity have been developed to specifically address these limitations and may improve clinical outcomes..

I. INTRODUCTION

Are a group of drugs whose main action is a pronounced and long-lasting reduction of stomach acid production. Within the class of medications, there is no clear evidence that one agent works better than another.

They are the most potent inhibitors of acid secretion available. This group of drugs followed and largely superseded another group of medications with similar effects, but a different mode of action, called H2-receptor antagonists. PPIs are among the most widely sold drugs in the world, and the first one, omeprazole, is on the WHO Model List of Essential Medicines. The cost between different agents varies significantly.

When activated by stimuli such as histamine and acetylcholine, the parietal cell undergoes dramatic morphologic changes from the resting status to the stimulated state. The gastric H,KATPase, which pumps gastric acid, appears to be in cytoplasmic tubular membranes in the resting state and then in the microvilli of the expanded secretory canaliculus in the stimulated state of the parietal cell. This morphologic change is proposed to result from fusion of cytoplasmic vesicles with the rudimentary microvilli to form the elongated microvilli of the expanded secretory canaliculus. The gastric H,K-ATPase moves from the tubulovesicles to the apical membrane in the canaliculus of the stimulated state and secretes gastric acid by an electroneutral, ATP-dependent hydrogen-potassium exchange. The enzyme uses extracellular K+ in order to secrete acid by the exchange of cytoplasmic hydronium with this K+. The cation reaches the luminal surface of the ATPase by insertion of K+ Cl− (KCNQ1, Clic6) channels into the microvillus membranee Proton pump inhibitors (PPIs) block the gastric H,K-ATPase, inhibiting gastric acid secretion.This effect enables healing of peptic ulcers, gastroesophageal reflux disease (GERD),

Barrett's esophagus, and Zollinger-Ellison syndrome, as well as the eradication of Helicobacter pylori as part of combination regimens. This article reviews the structure and function of the gastric H,K-ATPase and the inhibitors of this enzyme, the PPIs.

II. THE GASTRIC H,K-ATPASE:

The gastric ATPase is a member of the P2 type ATPases. The first step of the reaction is phosphorylation of the catalytic subunit by MgATP, with export of protons; this step is followed by luminal potassium-dependent dephosphorylation and potassium reabsorption. The result is electroneutral exchange of cytoplasmic protons for exoplasmic potassium.The gastric H,K-ATPase is composed of two subunits: a catalytic α subunit and a β subunit. The primary structure of the gastric H,K-ATPase α subunit was elucidated in the rat and then in the hog, rabbit, dog , and human. Functional studies demonstrated that ATP catalyzed an electroneutral exchange of H for K, with a variable stoichiometry of 2H/2K/ATP at pH 6.1, which fell to 1H/1K/ATP as luminal pH fell below 3.0.

The β subunit consists of 291 amino acids and contains six or seven N-linked glycosylation sites with one trans-membrane segment .The gastric H,K-ATPase is fully assembled during biosynthesis in the endoplasmic reticulum and is delivered to the apical membrane as a heterodimeric oligomer. N-glycosylation of the β subunit was identified as being responsible for trafficking to the canalicular membrane. The steady state distribution of the H,K-ATPase β subunit in polarized cells depends on the balance between direct sorting from the trans-Golgi network, secondary associative sorting with a partner protein, and selective trafficking .

In the α subunit, a cluster of intramembranal carboxylic amino acids, located in the middle of the transmembrane segments TM4, TM5, TM6, and TM8, contains the ion-binding domain in this enzyme, including a lysine 791. This lysine of the H,K-ATPase seems to characterize the H,K-enzyme specificity for outward transport of the hydronium ion. Movement of the R-NH3+ into the carboxylic ion-binding domain is thought to catalyze the export of protons to the luminal face of the pump. The functional form of the gastric H,K-ATPase is a [αβ]2 heterodimer oligomer .

The E1 form of the enzyme allows access to the ion-binding domain from the cytoplasmic surface. Binding of two ATP moieties, along with two magnesium ions, occurs in this conformation. One stabilizes the αβ orientation of the first two phosphates of the nucleotide, and the second, in proximity to the acceptor aspartyl residue, allows transfer of the γ phosphate to the catalytic subunit of the protein and initiates the change of conformation from the E1 form to the E1P conformer with the ion sites binding the hydronium ions. This process is followed by conversion to the E2P form, in which the protons are released outward and K+ binds from the luminal surface. The potassium occlusion site shows distorted octahedral geometry, with K+ bound predominantly on the M4 helix, with ligands contributed by backbone carbonyl oxygens of V338, A339, and V341, and by side chain oxygens of E820 and E795. Recently two hydronium transporting pathways were proposed. The hydroniums in the binding sites are transported into the lumen during the conformational transition from E1P to E2P.

III. EFFICACY OF INHIBITION OF ACID SECRETION:

. All of these drugs inhibit the gastric H,K-ATPase by covalent binding, so the duration of their effect is longer than expected from their levels in the blood. However, PPIs cannot inhibit all gastric acid pumps with oral dosing because not all pumps are active during the 90-minute half- life of the PPI in the blood. Because PPIs have a short half-life, only 70% of the pump enzymes are inhibited. It takes about 2 to 3 days to reach steady state inhibition of acid secretion.

The pump protein has a half-life of about 54 hours in the rat (and probably in humans). Thus about 20% of pumps are newly synthesized over a 24-hour period, and there may be greater pump synthesis at night than during the day. In addition, bedtime administration of PPIs will not add to inhibition of nocturnal acid breakthrough, because the drug will have disappeared by the time nighttime acid secretion is evident. Assuming that about 70% of pumps are activated by breakfast and that the PPI is given 30 to 60 minutes beforehand, it can be calculated that steady state inhibition on once-a-day dosing is about 66% of maximal acid output. Increasing the dose has virtually no effect once optimal dosage has been reached. Increasing the dose frequency does have some effect; a morning dose and an evening dose before meals results in about 80% inhibition of maximal acid output.

To improve acid inhibition, the plasma half-life of the PPI must be increased. One means is to replace the benzimidazole with imidazopyridine, slowing metabolism and prolonging the halflife of the drug, as found with tenatoprazole. This PPI has an advantage in suppressing nighttime acid secretion, but its slow activation blunts its advantage for daytime acid suppression. An alternative approach was to synthesize a slowly absorbed derivative of omeprazole, which then increased the plasma half-life about threefold and produced a median pH of about 5 in initial studies.

IV. STABILITY OF INHIBITION OF ACID SECRETION:

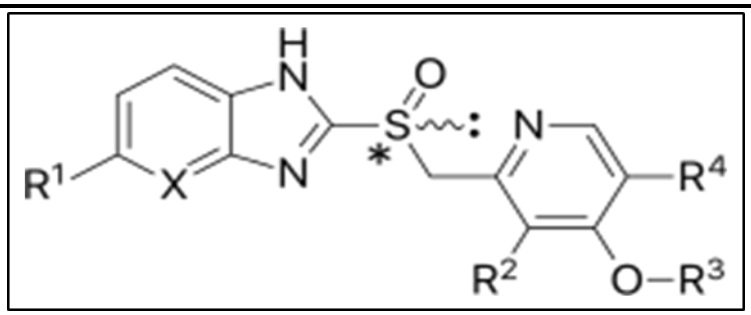
Beforey Reversal of inhibition of the ATPase can occur either by de novo synthesis or reduction of the disulfide bond between the PPI and the protein. A rationale for examination of reversal of covalent binding to the H,K-ATPase was provided by measurement of the half-life of pump protein biosynthesis in rats treated for 7 days with omeprazole, which was 54 hours, and the half- time of restoration of ATPase activity, 15 hours. Such data suggest a more rapid recovery of ATPase activity and acid secretion than would occur if only de novo biosynthesis was responsible for restoration of ATPase activit. In other experiments, the halftime of restoration of acid secretion in omeprazole-treated rats was 20 hours. An analysis ofthe rate of restoration of acid secretion in humans suggested that the half-time was 24 hours following omeprazole inhibition, whereas after pantoprazole it was 46 hours . Only pantoprazole appears to have a rate of recovery compatible with restoration of acid secretion due entirely to pump turnover.

V. CHEMISTRY AND BIOLOGY OF PPIS:

Because the H,K-ATPase is the final step of acid secretion, an inhibitor of this enzyme is more effective than receptor antagonists in suppressing gastric acid secretion . Timoprazole is a compound that inhibited acid secretion in vivo regardless of the nature of the stimulus, whether ligands acting via extracellular receptors such as histamine or acetylcholine or the intracellular second messenger, cyclic adenosine monophosphate (cAMP). This compound, a pyridylmethylsulfinyl benzimidazole, was synthesized in 1975. It was found that the compound was ineffective in the absence of acid transport by the ATPase. With acid transport in gastric ATPase vesicles, the drug inhibited acid production and ATPase activity.

It was therefore an acid-activated prodrug.

Omeprazole was subsequently synthesized, and in 1989 it became the first drug of this class to be introduced into clinical use. Omeprazole (Losec; AstraZeneca, Wilmington, DE) was followed by lansoprazole (Prevacid; TAP Pharmaceuticals, Lake Forest, IL), pantoprazole (Protonix; Wyeth Pharmaceuticals, Madison, NJ) or rabeprazole (Aciphex; Eisai Company, Woodcliff, NJ) and more recently by the S-enantiomer of omeprazole (Nexium, AstraZeneca). Typical structures of PPIs



Proton pump inhibitors-

PPIs are weak bases with a pKa1 between 3.8 and 4.9. This weak base pKa enables PPIs to accumulate selectively in the acidic space of the secretory canaliculus of the stimulated parietal cell, where the pH is about 1.0. This acid space–dependent concentration of PPIs is the first important property that determines their therapeutic index, giving a concentration at the luminal surface of the pump that is about 1000-fold higher than in the blood. The second step is acid-
dependent conversion from the accumulated prodrug to the activated species, which is a highly reactive thiophilic reagent. A second protonation of these compounds is required for their activation to the compounds that form disulfides with luminally accessible cysteines of the H,K- ATPase. The actual inhibitory form of these prodrugs is a tetracyclic sulfenamide or sulfenic acid. The order of acid stability is tenatoprazole > pantoprazole > omeprazole > lansoprazole > rabeprazole .

Depending on the difference of the substituents on the pyridine or benzimidazole, PPIs bind to different cysteines. Omeprazole binds at cysteine 813 and cysteine 892. Lansoprazole binds at cysteine 813 and cysteine 321. Pantoprazole and tenatoprazole bind at cysteine 813 and cysteine 822. With acid transport by the ATPase, the second proton is added and then the compound converts to the sulfenic acid. If this occurs rapidly, as for omeprazole or lansoprazole, reaction with cysteine 813 and/or cysteine 321 takes place, and no drug can access cysteine 822. However, if the activation is delayed, the drug can access cysteine 822 before activation to the sulfenic acid. Then, when activated, both cysteine 813 and 822 are derivatized, as found for pantoprazole or tenatoprazole.

Differences of PPI binding sites modify biologic activity. When the PPI-bound enzyme was treated with glutathione, an endogenous reducing agent with a concentration of about 3 mM in the parietal cell, omeprazole and pantoprazole differed in loss of PPI binding. Pantoprazole binding resists glutathione reduction. These observations suggest that removal of binding of the drug to cysteine 813 accounts for the fast phase of recovery of acid secretion; the slow recovery occurs because of a delay in removal of the drug from cysteine 822. Both residues, cysteine 813 and 822, are equally labeled by pantoprazole in vivo. The small amount of cysteine 822 bound by omeprazole in vivo is not seen in vitro, presumably because acidification in isolated gastric vesicles is less than occurs in vivo. In vivo, it is likely that a minor fraction of the omeprazole remains protonated at both the pyridine and benzimidazole nitrogen and is slowly activated, allowing some access to cysteine 822.

VI. MECHANISM OF ACTION:

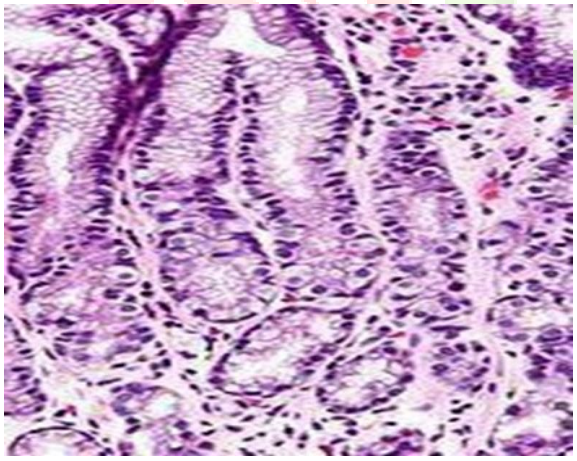
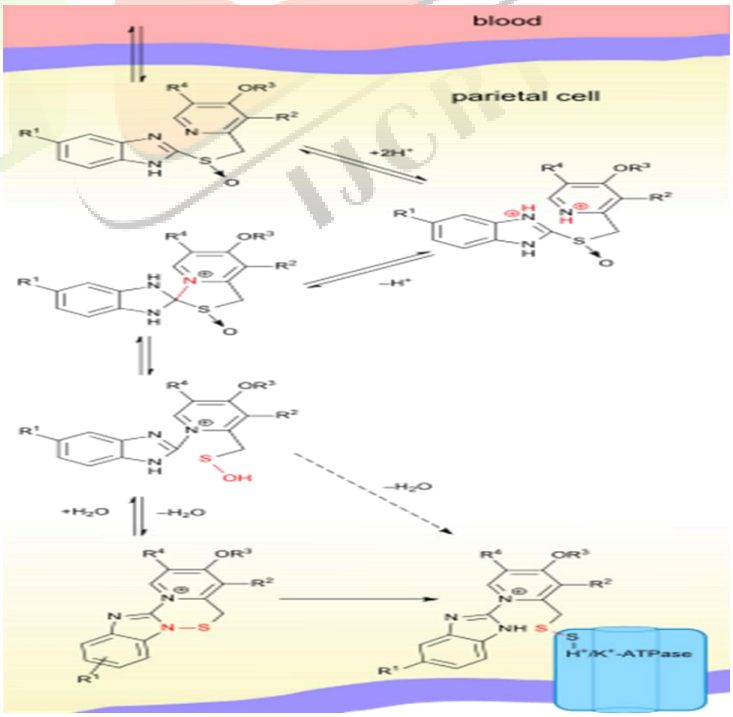


Fig. Micrograph of the gastric antrum showing G cell hyperplasia, a seen with PPI use (H&E stain).



Targeting the terminal step in acid production, as well as the irreversible nature of the inhibition, results in a class of drugs that are significantly more effective than H2 antagonists and reduce gastric acid secretion by up to 99%.

Decreasing the acid in the stomach can aid the healing of duodenal ulcers and reduce the pain from indigestion and heartburn. However, stomach acids are needed to digest proteins, vitamin B12, calcium, and other nutrients, and too little stomach acid causes the condition hypochlorhydria.

The PPIs are given in an inactive form, which is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) with acidic environments. In an acid environment, the inactive drug is protonated

and rearranges into its active form. As described above, the active form will covalently and irreversibly bind to the gastric proton pump, deactivating it.

VII. PHARMACOKINETICS AND PHARMACODYNAMICS OF PROTON PUMP INHIBITOR

The rate of omeprazole absorption is decreased by concomitant food intake. In addition, the absorption of lansoprazole and esomeprazole is decreased and delayed by food. It has been reported, however, that these pharmacokinetic effects have no significant impact on efficacy.

PPIs have a half-life in human blood plasma of only 60–90 minutes, but because they covalently bind to the pump, the half-life of their inhibition of gastric acid secretion lasts an estimated 24 hours. Dissociation of the inhibitory complex is probably due to the effect of the endogenous antioxidant glutathione which leads to the release of omeprazole sulfide and reactivation of the enzyme.

It is clear that the quantity of PPI bound to the enzyme is directly linked to the inhibition of gastric acid secretion. However, it is very difficult to measure the quantity of PPI binding in vivo, so we need another parameter substituting the quantity of PPI binding. As discussed above, the plasma level of the drug was not linear to the inhibitory activity. It was, however, observed that the gastric antisecretory effect was related to the total dose and AUC, whereas the peak level or the shape of the curve was of minor importance. This enables AUC to correlate with the activity.

However, this relationship is only acceptable up to a certain level such as the ED50 level of dosage. Linear relationship between the inhibitory activity and AUC was not shown at higher dosage of the drug. Though the relationship between AUC and the inhibition was not linear at higher dosage of the drug due to the short half-life of the drug and the limited exposure of the enzyme to the drug, at least AUC showed the efficacy of the drug with good reliability. Unlike the animal model, the measurement of inhibition of acid output in human is not easy, so measuring intragastric pH is used to present the inhibition due to drug activity.

Actually, control of the intragastric pH is very important in healing acid-related diseases and eradicating Helicobacter pylori.

The duration time of intragastric pH over 3 is crucial for healing duodenal ulcers. In order to get successful treatment of GERD, percent time of the intragastric pH $>$ 4 should be high, 43 as is true for eradicating H. pylori. Therefore, duration time of intragastric pH over 3 or 4 and mean (or median) intragastric pH become powerful tools in evaluating the drug's efficacy. Mean intragastric pH was shown to have some linearity with AUC, however, the degree of acid suppression shown by intragastric pH profile would be the best in vivo parameter with which to compare the potency of PPIs. All PPIs have about 1 hour of the elimination half-life, but the time to maximum plasma concentration (tax) was widely deviated from 1 hour to 5 hours by drug formulation and/or food effect.

Examples

Medically used proton pump inhibitors:

- Omeprazole (OTC in the USA)
- Lansoprazole
- DE lansoprazole
- Esomeprazole
- Pantoprazole
- Rabeprazole
- Liarozole (not FDA approved as of May 2017)

VIII. MEDICAL USES:

These drugs are used in the treatment of many conditions, such as:

- Dyspepsia
- Peptic ulcer disease including after endoscopic treatment for bleeding
- As part of Helicobacter pylori eradication therapy
- Barrett's esophagus
- Eosinophilic esophagitis
- Stress gastritis and ulcer prevention in critical care
- Gastronomes and other conditions that cause hypersecretion of acid including Zollinger–
- Ellison syndrome (often 2–3x the regular dose is required)

Specialty professional organizations recommend that people take the lowest effective PPI dose to achieve the desired therapeutic result when used to treat gastroesophageal reflux disease long-term. In the United States, the Food and Drug Administration has advised that no more than three 14-day treatment courses should be used in one year.

Despite their extensive use, the quality of the evidence supporting their use in some of these conditions is variable. The effectiveness of PPIs has not been demonstrated for every case. For example, although they reduce the incidence of esophageal adenocarcinoma in Barrett's esophagus, they do not change the length affected.

IX. ADVERSE EFFECTS:

In general, proton pump inhibitors are well tolerated, and the incidence of short-term adverse effects is relatively low. The range and occurrence of adverse effects are similar for all of the PPIs, though they have been reported more frequently with omeprazole. This may be due to its longer availability and, hence, clinical experience.

Common adverse effects include headache, nausea, diarrhea, abdominal pain, fatigue, and dizziness. Infrequent adverse effects include rash, itch, flatulence, constipation, anxiety, and depression. Also infrequently, PPI use may be associated with occurrence of myopathies, including the serious reaction rhabdomyolysis.

Long-term use of PPIs requires assessment of the balance of the benefits and risks of the therapy. Various adverse outcomes have been associated with long-term PPI use in several primary reports, but reviews assess the overall quality of evidence in these studies as "low" or "very low".They describe inadequate evidence to establish causal relationships between PPI therapy and many of the proposed associations, due to study design and small estimates of effect size. Benefits outweigh risks when PPIs are used appropriately, but when used inappropriately, modest risks become important. They recommend that PPIs should be used at the lowest effective dose in people with a proven indication, but discourage dose escalation and continued chronic therapy in people unresponsive to initial empiric therapy.

Nutritional-

Gastric acid is important for breakdown of food and release of micronutrients, and some studies have shown possibilities for interference with absorption of iron, calcium, magnesium, and vitamin B12. With regard to iron and vitamin B12, the data are weak and several confounding factors have been identified.

Low levels of magnesium can be found in people on PPI therapy and these can be reversed when they are switched to H2-receptor antagonist drugs.

High dose and/or long-term use of PPIs carries a possible increased risk of bone fractures which was not found with short-term, low dose use; the FDA included a warning regarding this on PPI drug labels in 2010.

Gastrointestinal-

Some studies have shown a correlation between use of PPIs and Clostridium difficile infections. While the data are contradictory and controversial, the FDA had sufficient concern to include a warning about this adverse effect on the label of PPI drugs. Concerns have also been raised about spontaneous bacterial peritonitis in older people taking PPIs and in people with irritable bowel syndrome taking PPIs; both types of infections arise in these populations due to underlying conditions and it is not clear if this is a class effect of PPIs.PPIs may predispose an individual to developing small intestinal bacterial overgrowth or fungal overgrowth.

Long-term use of PPIs is associated with the development of benign polyps from fundic glands (which is distinct from fundic gland polyposis); these polyps do not cause cancer and resolve when PPIs are discontinued. There is no association between PPI use and canceror pre-cancer.There is concern that use of PPIs may mask gastric cancers or other serious gastric problems and physicians should be aware of this effect. PPI use has also been associated with the development of microscopic colitis.

There is also evidence that PPI use alters the composition of the bacterial populations inhabiting the gut. Although the mechanisms by which PPIs cause these changes are yet to be determined they may have a role in the increased risk of bacterial infections with PPI use.

Cardiovascular-

Associations of PPI use and cardiovascular events have also been widely studied but clear conclusions have not been made as these relative risks are confounded by other factors.PPIs are commonly used in cardiovascular patients for gastric protection when aspirin is given for its antiplatelet actions. An interaction between PPIs and the metabolism of the platelet inhibitor clopidogrel is known and this drug is also often used in patients with cardiac disease.

One suggested mechanism for cardiovascular effects is because PPIs bind and inhibit dimethylargininase, the enzyme that degrades asymmetric dimethylarginine (ADMA), resulting in higher ADMA levels and a decrease in bioavailable nitric oxide.

Other-

Associations have been shown between PPI use and an increased risk of pneumonia, particularly in the 30 days after starting therapy, where it was found to be 50% higher in community use. Other very weak associations of PPI use have been found, such as with chronic kidney disease and dementia.As these results were derived from observational studies, it remains uncertain whether such associations are causal relationships.

X. PROTON PUMP INHIBITOR KIDNEY PROBLEMS:

Proton Pump Inhibitors (PPI) work by reducing the amount of stomach acid produced, reducing symptoms of heartburn and pain caused if stomach juice backs up into the esophagus. This also allows the esophagus to heal.

Medications like Nexium, Prilosec, Protonix and others have been used by millions of Americans, generating billions in revenue each year for the drug makers. However, concerns have existed for years that the PPI drugs are widely overused, often without re-evaluation to determine the need for continued treatment or any attempts to reduce

XI. CONCLUSIONS:

The PPIs are prodrugs. These prodrugs require gastric acid secretion to be converted to the active sulfenamide or sulfenic acid that blocks gastric acid secretion. All PPIs except tenatoprazole have short half-lives (about 1 hour) and all have good oral bioavailability. Most PPIs are metabolized by CYP2C19 and 3A4. Hepatic impairment and old age reduce clearance of the PPIs, as do mutations in CYP2C19. Acid suppression studies comparing omeprazole, lansoprazole, rabeprazole, and pantoprazole show equivalent efficacy. Most studies using standard doses have not shown a significant difference between the four PPIs for

the healing of reflux esophagitis or duodenal ulcer. Esomeprazole and tenatoprazole have stronger acid suppression, with a longer period of intragastric pH greater than 4.

Acute Interstitial Nephritis-

Evidence suggests that proton pump inhibitors increase the risk of acute interstitial nephritis, which involves inflammation of the kidneys that may lead to chronic and long-term injury if the drug is not discontinued.

Acute Kidney Injury-

In April 2015, a study published in the medical journal CMAJ Open highlighted the risk of acute kidney injury with proton pump inhibitors.

Researchers from the Institute for Clinical Evaluative Sciences and St. Michael's Hospital in Toronto examined data on 300,000 older individuals and found that those who started PPI drugs had a 2.5 fold increased risk of acute kidney injury, as well as 3 times higher risk of acute interstitial nephritis when compared to individuals who did not use the drugs.

Acute kidney injury involves the abrupt loss of kidney function, which may occur after taking a PPI drug. While many individuals regain normal kidney function.

Chronic Kidney Disease-

Chronic kidney disease from proton pump inhibitors may cause wastes to build up to high levels in the blood, which may eventually lead to kidney failure, the need for life-long dialysis treatments or a kidney transplant surgery.

XII. Acknowledgment

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