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PPI INDUCED RENAL TOXICITY

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Abstract:

PPIs are mostly used drugs in many prescriptions along with drugs for other co-morbidities and also used for long time periods and as OTC drugs (medication). These drugs on prolong use causes renal toxicity in many cases by affecting glomerular filtration and also through several cases like increase in pH, gastroenteritis, hyperplasia, hypertrophy, hypergastrinemia, hyperchlorhydria, and effect on mitochondrial cells. The unrequited actions by PPIs also can appear in paediatrics along with adults. In this paper we will review about brief information regarding pharmacokinetics and pharmacodynamics of proton pump inhibitors and those several adverse pathways, physiologies and the alternative to prevent these conditions.

Keywords: *Glomerular filtration, hyperplasia, hypertrophy, hypergastrinemia, hyperchlorhydria.*

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INTRODUCTION:

Kidney the excretory organ of body, plays a major role in maintaining homeostasis mainly through large amount of blood supply and of enormous surface area of renal tubular epithelium, because of this most drugs are passing through kidneys. The parts of kidney that involved in toxic nephropathies are glomerular, tubular, interstitial (or) vascular lesions. These lesions may be toxic (or) immunologic. Alterations in tubular cells may also occur.

Now a day's antibiotics are the commonly used drugs for all age groups, in any therapy regimens and in infections to cure (or) to prevent the chances of infections. The chance of infection is increased on using many medications by decline our immune system power. Based on the action of antibiotics, most drugs act on cell walls, floral line, and bacteriostatic action by changing pH, because of this entire actions GI tract is affected with ulcers like peptic ulcers, duodenal ulcers, gastric oesophagus reflux disease. For this antacids (PPI) are mostly prescribed and used. But these PPIs have some effects like tubulointerstitial nephritis, atherosclerosis, and risk in reduced liver function, pancreatitis, and erythema multiforme. PPI use is associated with a higher risk of incident CKD. [1]

KIDNEY AND ITS FUNCTION:

Kidneys are bean shaped organs located at the back of the abdominal cavity in retroperitoneal space. Kidneys have a pair of arteries and veins from which kidney receives blood and blood exits from kidney and attached to ureter, a tube that carries excreted urine to bladder. [2,3] The size of kidney varies in men and women; those are in men- right kidney 11.4cm length, 6.5cm width and left kidney 12.0cm length, 6.7cm width and in women- right kidney 10.8cm length, 5.9cm width and left kidney 11.6cm length, 6.0cm width. Based on overall observation right kidney is smaller than left kidney in size. [4]

The nephron is the microscopic structural and functional unit of kidney, and composed of Renal corpuscle, Glomerulus, Bowman's capsule, Renal tubule. [2,3] Renal corpuscle involves in filtration of blood plasma. Corpuscle has 2 poles- vascular pole and urinary pole. Blood enters and leaves from kidney through vascular pole and glomerular filtrate leaves through urinary pole. Glomerulus is a filtering capillaries located at vascular pole in Bowmen's capsule. Only about a fifth of the plasma is filtered in the glomerulus. The rest passes into an afferent arteriole. The Bowmen's capsule composed of inner layer with podocytes and outer layer with simple squamous epithelium. The glomerular filtrate is fluids from blood in glomerulus next moves to renal tubule, further processed to form urine/tubular fluid. [5] Renal tubule is the portion of nephron contains tubular fluid, after passing through this, filtrate continues to collecting duct system. [6,7] Renal tubule consists of proximal convoluted tubule, loop of henle, distal convoluted tubule and connecting tubule. Proximal convoluted tubule located in cortex and helps to increase the area of absorption. Loop of henle is located in medulla containing 2 segments ascending and descending loops and the main role is to concentrate the salt in the interstitium (the tissue around the loop). The distal convoluted tubule is a place where ATP (energy) is produced for take place of active transport. The main function is ion transport which is regulated by the endocrine system. [8-10]

FATE OF DRUGs ON KIDNEY:

Modified tubular cells – Toxins alter the cells at multiple sites leads to toxic by-products. Toxins act on phospholipid metabolism in tubular cells and convert that cycle to deliver lysophospholipids and free fatty acids, which have toxic properties.

Cell injury – Cell injury and necrosis is mainly caused due to increased levels of calcium in blood. This may include mitochondrial membrane permeability alterations, activation of specific ion channels, increase (or) decrease enzymatic actions, formation of kidney stones, increase cellular contractile components, induce modifications (or) cytoskeleton. [11]

PROTON PUMP INHIBITORS:

PPI inhibits secretion of H^+ ions from parietal cells in intestinal flora, thus decrease the formation of acid. Because of the last step inhibition in gastric acid secretion regardless of the acid secretion stimulus, PPIs gained popularity and can be dosed once a day in most patients. [12]

Available proton pump inhibitors include:

- Omeprazole (Prilosec, Prilosec OTC)
- Aspirin and omeprazole (Yosprala)
- Lansoprazole (Prevacid, Prevacid IV, Prevacid 24-Hour)
- Dexlansoprazole (Dexilent, DexilentSolutab)
- Rabeprazole (Aciphex, Aciphex Sprinkle)
- Pantoprazole (Protonix)
- Esomeprazole (Nexium, Nexium IV, Nexium 24 HR)
- Esomeprazole magnesium/Naproxen (Vimovo)
- Omeprazole/Sodium bicarbonate (Zegerid, Zegerid OTC)

The most common side effects of proton pump inhibitors are:Headache, Diarrhoea, Constipation, Abdominal pain, Flatulence, Fever, Vomiting, Nausea, Rash.

MECHANISM OF ACTION:

The first proton pump inhibitor used clinically was 2-[(3, 5-dimethyl-4-methoxypyridin-2-yl) methylsulfinyl]-5-methoxy-1H-benzimidazole, omeprazole. [13] This compound is a weak base ~pka 4. The H＋, K＋-ATPase in the parietal cell secretes acid into the secretory canaliculus generating a pH of ＜ 1.0 in the lumen of this structure. The acidity of this space allows accumulation of weak bases of this pka. Secretions with pka less than 4.0 can accumulated only in this acidic space and can not in any other spaces in the body. Then, this compound is rapidly activated by the high acidity by binding to the cysteines which are accessible to the activated form leads to inhibit acid secretion. [14-17] The binding sites of omeprazole are Cys813 and Cys892. [18]

Other covalent binding inhibitors belonging to the substituted benzimidazole family were followed, Lansoprazole reacts with Cys813 and Cys321, these being in the luminal vestibule, whereas pantoprazole reacts with Cys813 and Cys822. [17] [19,20]

METABOLISM:

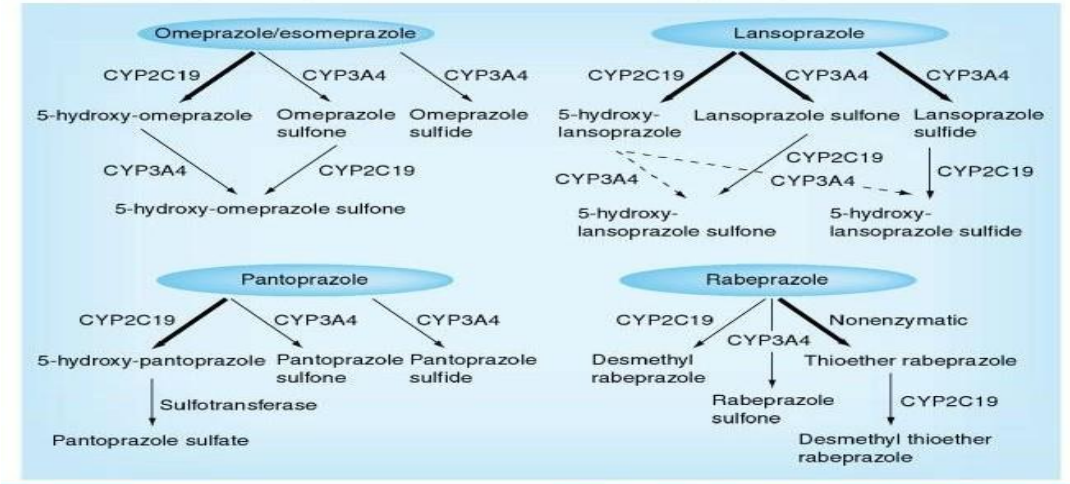

Figure 1: Metabolic pathways of different Proton Pump Inhibitors

CYP iso-enzymes are participating in the metabolism of all PPIs. The thickness of the arrows indicates the extent to which the different CYP iso-enzymes contribute to the metabolism of omeprazole and of other PPIs.

EXCRETION:

PPIs are not excreted directly in urine. Its metabolites excreted 80% through urine, 20% through faeces.

Table 1: Pharmacokinetic properties of proton pump inhibitors

Parameter	Omeprazole 20mg	Lansoprazole 30mg	Pantoprazole 40mg	Rabeprazole 20mg	Esomeprazole
C_{max} (µmol/L)	0.23-23.2	1.62-3.25	2.87-8.61	1.14	2.1-2.4 at 20mg, 4.7-5.1 at 40mg
V(L/kg)	0.13-0.35	0.4	0.15	0.34	0.22-0.26
CL(ml/min)	400-620	400-650	90-225	90	160-330
$t_{1/2}$ (hr)	0.5-1.2	0.9-2.1	0.8-2.0	0.6-1.4	1.3-1.6
Mean % of time (pH>4)		60%	51%	77.0-84.1%	42%

t_{max}time to maximal plasma concentration; C_{max}maximal plasma concentration; AUC area under the plasma concentration curve; V apparent volume of distribution; CL clearance; $t_{1/2}$ elimination half-life. [21]

PPI EFFECTS ON KIDNEY:

Majorly the two main effects are AIN (Acute interstitial nephritis), TIN (Tubulointerstitial nephritis). AIN is an important cause of acute renal failure resulting from immune-mediated tubulointerstitial injury. In AIN creatinine levels increased majorly and creatinine could potentiate hypoglycaemia, hypertension, DVT, kidney stones, migraines. [22] TIN involves the immune mediated infiltration of the renal tubules and interstitium by inflammatory cells resulting in decreased renal function. [23]

1. The common ADRs of PPI are headache, nausea, diarrhoea, abdominal pain, fatigue, and dizziness. Long term use of PPI can cause severe condition of these symptoms leads to gastroenteritis resulting various infections. Due to these infections WBC count increase in body and moreover prolonged use of PPI causes decreased intestinal acidic level and can permanently alter the pH. Thus intestinal flora get damaged and increase in inflammatory cytokines and lymphocyte levels. These result in more chances of clotting factors leading to clotting. In this process clotting factor-IV (Calcium) also increases and this increased calcium levels result in damage of kidneys by interrupting renal tubular cell functioning through mitochondrial cycle cause cell injury/necrosis. **Calcium effect on mitochondria of cell:** excess calcium uptake by mitochondria triggers a bioenergetics failure of the organelle through the opening of the permeability transition pore, release of cytochrome C and of other proapototic factors and cellular death by apoptosis/necrosis by mitochondrial calcium homeostasis. [24,25]
2. In patients without Helicobacter pylori infection, the prolonged use of PPIs actually produces parietal cell hypertrophy and hyperplasia, resulting in an effectively increased parietal cell mass. It is likely that the parietal cell hyperplasia and hypertrophy observed with Omeprazole, Lansoprazole is due to a trophic effect resulting from the hypergastrinemia associated with the hyperchlorhydria induced by PPI. It also provides a physiological basis for the rebound hyperchlorhydria transiently associated with cessation of therapy with PPI. [26]
3. In case of patients with Helicobacter pylori infection, after longterm PPI administration intestinal pH increases and patient get resistance to PPI. This may cause gastric ulcers, infections in one case and might make enzymes less effective in stomach in another case. Imbalance of enzymes causes effect on liver and alterations in CYP2C19 and CYP3A4 coenzymes resulting abnormal metabolism of PPIs and produce toxic compounds those result in renal toxicity. [26,27]
4. GFR rate decreased with PPI when compared with H_2 blockers. PPIs have incident harm. PPI group had a lower GFR right from the start. The p-value was < 0.001. Stratified against PPI use, they were all at higher exposures to things like antihypertensive, diuretics, aspirin and statins. These are all high-risk disease states that are associated with renal disease. (like hypertension p-value < 0.001, CVD p-value = 0.003) [28] PPI users had an excess risk for chronic renal outcomes compared with those taking H2 blockers. Specifically, their risk was 22% higher for incident eGFR less than 60 mL/minute/1.73 m^2 (HR, 1.22; 95% CI, 1.17 - 1.27), 29% higher for CKD (HR, 1.29; 95% CI, 1.22 - 1.36), 26% higher for a greater than 30% decrease in eGFR (HR, 1.26; 95% CI, 1.19 - 1.32), and 35% higher for ESRD or a greater than 50% decrease in eGFR (HR, 1.35; 95% CI, 1.19 - 1.53).In each case, the researchers calculated that slightly less than half (44.7% - 46.7%) of the risk for the chronic kidney conditions was mediated by AKI. [29]
5. PPIs may also alter the phospholipid metabolism in cells and produce lysophospholipids and free fatty acids by prolonged use which has toxic detergent properties. And these toxic compounds when excreting trough kidneys can damage filtration and secretion parts leads to renal failure.

Table 2: PPI pharmacokinetics in effected patients:

Parameter	Omeprazole 20mg	Lansoprazole 30mg	Pantoprazole 40mg	Rabeprazole 20mg	Esomeprazole
C_{max} (µmol/L)	2.3-34.3	5.3-7.45	3.45-12.67	5.46	6.9-7.6 at 20mg, 6.8-8.7 at 40mg
V(L/kg)	0.03-0.15	0.02	0.09	-	0.12-0.16
CL(Ml/min)	250-310	220	70	-	110
$t_{1/2}$ (hr)	0.5-1.2	0.9-2.1	0.8-2.0	0.6-1.4	1.3-1.6
Mean % of time (pH>4)	-	60%	-	77.0-84.1%	42%

PPI effects in paediatric on prolong use:

The frequency of use of PPIs was lansoprazole >omeprazole>pantoprazole>esomeprazole>rabeprazole. Most are dosed twice/day. Parietal cell hyperplasia was observed in 0-16%, gastric histology was normal significantly more often when treatment continued for longer than 48months and when patients were treated with higher doses. Gastrin levels were elevated to >90 pg/ml in 73% children but vit-B_{12} remained normal. [12]

ALTERNATE:

At initial stages parietal cell hypertrophy is entirely reversible and that parietal cell architecture returns to normal within 3 months of discontinuing PPIs. [26] 18.24% of new PPI users developed AKI during period compared with 12.67% of new users of H_2 blockers and PPI have an increased risk of an estimated glomerular filtration rate under 60ml/min/1.73m^2 when compared with H_2 blockers. [30,31] Histamine can be released by the enterochromaffin like cells directly (or) after stimulation of these cells by gastrin, which is released after a meal, histamine then binds to the H_2 receptor and stimulates H^+K^+- ATPase to release intracellular second messengers, cyclic adenosine monophosphate and Ca^{2+}, leading to acid release. [12,17]

CONCLUSION:

PPIs are the mostly used drugs in the treatment of GI tract disturbances. Prolong use of these drugs can cause harm to kidneys, process of coagulation and even to gastro intestine also. So it is much better to switch from PPIs to H_2 blockers in sometimes according to the patient's condition. It is better to use PPIs whenever necessary up to the relief of symptoms appear, after that life style modifications are good to avoid those GI disturbances and also to avoid unrequited health changes.

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