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TOXICOLOGY: A PILOT STUDY ON IMPACT OF LONG TERM USE OF HIGH DOSE PPIs ON RENAL HISTOLOGY AND RENAL FUNCTION TESTS ON RABBIT MODEL

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Abstract:

. A very well-known group of drugs for reducing the acid peptic disease is PPIs (Proton Pump Inhibitors). The adverse effect profile of these agents is a topic of research and discussions in various countries that led to careful usage recommendations from the FDA. We tried to explore the renal toxic effects of these agents at higher doses in rabbit model in a pilot study using very small sample. We found some disturbance in normal renal histology, like inflammatory infiltrations, vacuolization, micro calcifications and some hyaline changes were also observed. Renal functions were also deranged with normal creatinine levels at 0.5 mg/dl and 0.8mg/dl near to control group 0.6 mg/dl but raised serum urea was found as 57mg/dl and 67mg/dl for Esomeprazole and Pantoprazole respectively much higher than the 36mg/dl of the control group similarly Serum electrolytes were also much deranged by both drugs.

Conclusion: *Disturbance in normal renal histology occurred along with renal functions and serum electrolyte abnormalities following long term use of higher doses of PPIs in study animals.*

Key Words: *Urea, Creatinine, PPIs, histology.*

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INTRODUCTION:

Toxicology has multidimensional aspects from pharmacology to forensic medicine for various substances of daily life use .It has been more than 30 years Proton Pump Inhibitors are available in the market and being used for multiple GI disorders. Omeprazole was the first discovered agent of this class in 1989 followed by other drugs like esomeprazole, rabiprazole and pantoprazole etc [1]. The superiority of PPIs over H2 blockers lies in their complete blockage of HCL synthesis by the stomach parietal cells [2,3]. These agents need enteric coating owing to their acid unstable nature to skip the stomach and reach the duodenum to get absorbed with a bioavailability of 30-90%, their metabolism cytochrome P450 dependent specially CYP2C19 and CYP3A4 isozymes [4]. These drugs are prodrugs so must be activated for effectiveness. These agents are available in oral and parenteral form and inhibit >90% acid secretion at standard doses. Their metabolites are excreted through kidneys and feces [5]. Achlorhydria, fracture tendency, B12 deficiency, hypomagnesemia and pneumonia are some well stablished side effects of this class of drugs [6-8]. PPIs are derived from benzimidazole and contain heterocyclic structure with a pyridine linked through a methylsulfinyl group with the benzimidazole moiety [9].This current study was directed to evaluate the effects of Esomeprazole and Pantoprazole on the serum urea, creatinine, electrolytes and serum albumin on the rabbit model. Hopefully current study will ease the path for other researchers to work out these effects in human subjects.

METHODOLOGY:

After purchasing male rabbits from Hyderabad market animals were kept in separate cages and weighed. Acclimatization was done for 1 week under controlled environment with provision of normal food and water .PPIs used were esomeprazole and pantoprazole given orally at 40mg/day (human dose) for a period of 2 months after which rabbits were scarified collecting blood samples for serum urea, creatinine and electrolytes while organs were saved in formalin for histological examination. There were six rabbits 2 /group 1 from each esomeprazole and pantoprazole group after 1 month. Lab test were performed on remaining rabbits in Isra University research laboratory and histological examination took place at anatomy department.

RESULTS:

There were many changes seen on renal histology of rabbits on PPIs treatment including the inflammation, vacuole formation, micro calcification and hyaline changes. Renal functions tests were also abnormal, creatinine levels in control group was 0.6 mg/dl while in esomeprazole group it was 0.8mg/dl whereas it 0.5mg/dl in pantoprazole group that was with in norms. Serum urea was 57mg/dl in pantoprazole group, 67mg/dl in esomeprazole group and 36mg/dl in control group that was much high in comparison to control. Electrolyte changes were seen both Esomeprazole as well as Pantoprazole groups shown in table 2 respectively however serum albumin levels remained unaffected

Table.1 Serum Urea, Creatinine and Albumin levels in study animals

S. No	Parameters	Normal	Esomeprazole	Pantoprazole	P-Value
1.	Serum Urea	36mg/dl	67mg/dl	57mg/dl	Not calculated
2.	Serum Creatinine	0.6mg/dl	0.8 mg/dl	0.5mg/dl	
3.	Serum Albumin	3.7gm/dl	4.3gm/dl	3.9gm/dl	
Note: Statistical tests were not applied due to very small sample size					

Table.2 Serum electrolytes in study animals

S. No	Parameters	Normal	Esomeprazole	Pantoprazole	P-Value
1.	Serum Sodium	117 mmol/L	98mmol/L	91 mmol/L	Not Calculated
2.	Serum Potassium	4.2 mmol/L	6.7mmol/L	7mmol/L	
3.	Serum Chloride	101 mmol/L	68mmol/L	91 mmol/L	
4.	Serum Bicarbonate	13 mmol/L	12mmol/L	12 mmol/L	
Note: Statistical tests were not applied due to very small sample size					

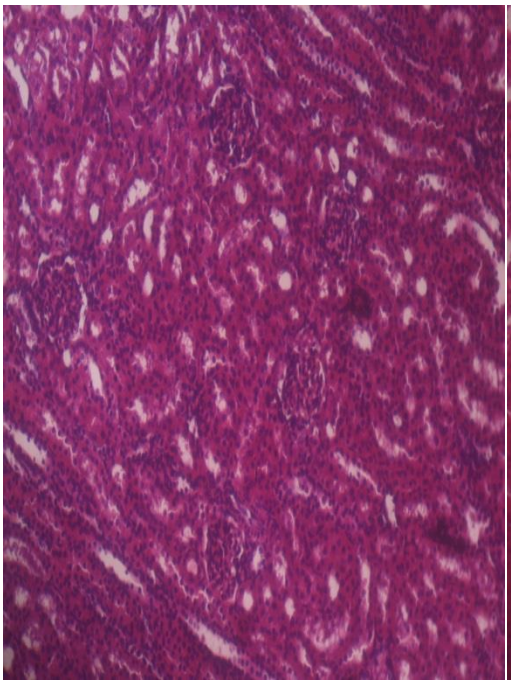

Figure1A. Renal Histology of PPI Treated Rabbit

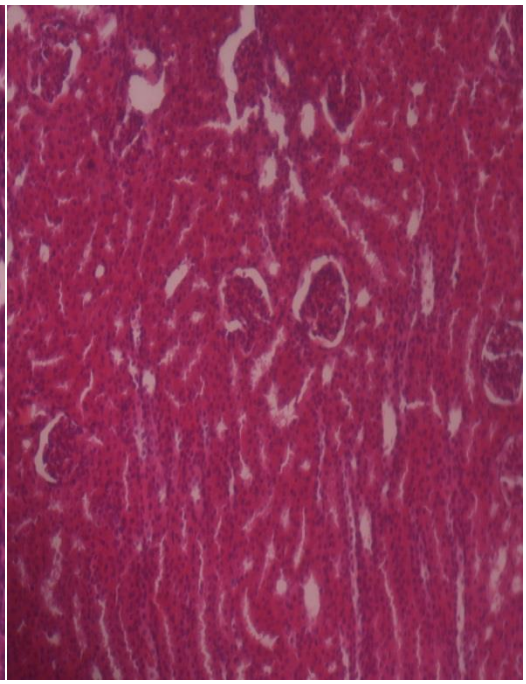

Figure1B. Normal Renal Histology

DISCUSSION:

Recent researches by Pradeep Arora et al (2016) and Yan Xie et al (2017)suggested chronic PPIs use to be a cause of chronic kidney disease among 20%-50% users but in our pilot study we could not find such observation with normal renal function tests this inconsistent difference between these studies may be due to species difference or our sample was so small that might have caused this but the histology does point towards some progressive harm in the form of inflammation [10,11]. Electrolyte imbalance related with long term PPIs use is a well-established fact with hypomagnesemia, hypokalemia and hypocalcemia, later being the a risk factor for bone fractures is of clinical significance specially in old age [12,13]. We observed hyperkalemia in the rabbits on PPIs and hyponatremia and hypochloremia no major difference was seen between esomeprazole and pantoprazole, this observation suggests that PPIs do have some effect on kidneys that requires further evaluation. The pattern of PPIs induced injury is believed to be mediated through reduction in the nitric oxide production along with some anti-oxidants depletion [14,15].Another mechanism described for PPIs induced damage is endothelial injury and loss of lysosomal functions so cells lose their defensive power[16,17]. The changes in renal histology like inflammation and vacuolization are attributed to cell injury while micro calcification we think were as a consequence of excessive renal excretion of Ca however the hyaline changes were not understandable for us weather caused by PPIs or some other pathology was going on in the study animal previously as the sample size was very small due to pilot project while death of animal might be from hyperkalemia. So we recommend large sample study to confirm the findings of our study. We could not evaluate the mechanism behind these effects of PPIs so further studies are recommended on larger sample covering various parameters like oxidative stress etc.

CONCLUSION:

PPIs disturbed the renal histology and functions at higher doses in this animal model pilot study.

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