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ANALYSIS OF EFFECTS OF ACID SUPPRESSION THERAPY ON RENAL TISSUE USING EXPERIMENTAL ANIMAL.

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ABSTRACT… Objectives: To analyze the effects of acid suppression therapy by proton pump inhibitors on renal tissue by using mice as experimental animal. **Study Design:** Randomized control trial. **Setting:** Animal house of University of Sargodha. **Period:** 6 weeks (From 1st January 2018 to 15th February 2018). **Material and Methods:** The sample consisted of 60 mice. Simple Random Sampling was the technique which was used for the sampling procedure. The mice were procured from Veterinary University Lahore Punjab. The animals were handled according to the international standards of environmental and ethical conditions. The animals were divided into three groups. One group was labeled as control group for comparison and the other groups served as experimental. The histological study was done to analyze the effects of proton pump inhibitors. **Results:** Histological analysis of the sections made from the renal tissue revealed that acid suppression therapy given in the form of proton pump inhibitors induced toxic effects on the kidneys. The glomerulus was observed to be congested along with cellular infiltrate in the interstitium.

Key words: Cellular Infiltrate, Congestion, Renal Toxicity, Acid Suppression Therapy.

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INTRODUCTION

Peptic ulcer is the break in the lining of stomach or initial portion of small intestine.[1] Peptic ulcer is present in almost 4% of the population.[2] About 10 percent of the people develop peptic ulcer at some stage of their life.[3] The first causative agent for it identified was as H. Pylori in late twenty century.[4] The first complication of this disease as perforated peptic ulcer was observed in 1670 in a princess of England.[5] Peptic ulcer disease tremendously affected the morbidity and mortality till the last decades of 20th century.[6] The impressive fall in its incidence was because of introduction of acid suppressant medication. They resulted in 267,500 deaths in 2015 down from 327,000 in 1990.[7]

As recently as 1970, primary option for its treatment was surgery.[8] The advent of Histamine blockers in 1970 and Proton Pump Inhibitors in 1980 revolutionized the management by reducing the surgical intervention. Both suppress the acid secretion.[9] PPI therapy became the preferred option because of the greater effectiveness. They are among the most frequently prescribed medicine all over the world.[10] They are thought to be the safe therapy but nowadays, their use on long term basis without any reevaluation is common.[11] It has led to many adverse effects. In relation to kidney, PPI therapy is considered to be associated with acute kidney injury and progression to chronic kidney disease.[12]

In 1992, first case report of acute interstitial nephritis was published along with the use of PPI.[13] Following decade showed many isolated cases. In 2006, biopsy proven case series of this toxicity was reported.[14] There is a strong observational evidence of association between PPI therapy and the development of renal toxicity. It is reported in almost 15% of the cases of acute renal failure.[15] Because of the extensive blood circulation through kidneys, the renal parenchymal cells are exposed to drug metabolites and thus they are at greater risk of developing drug toxic effects.[16] Various hypotheses have been put forward to explain the possible cause of drug induced renal toxicity like glomerular injury, hemodynamic pathology and the tubular cell involvement.[17] It is also thought that oxidative stress might be involved in kidney damage.[18]

For the purpose of study, Omeprazole was used which belonged to the group of PPI. After its introduction in 1989, it is widely prescribed for the gastrointestinal disorders.[19] Within this class of drug, all basically act as acid suppressants to maintain the intragastric pH above 6 and there is no major difference in their effiency.[20] The renal toxicity is observed as congestion of blood vessels, hemorrhage and infiltration of inflammatory cells.[21] Continued use of the drug has been linked with the progression of the disease in the form of chronic renal damage.[22]

MATERIAL AND METHODS

Sixty mice were procured from the Veterinary University Lahore Punjab. They were divided into Group A for control animals and Group B and C for the experimental process. They were kept in separate labeled cages under standard conditions of temperature and humidity. After acclimatization of animals, the procedure was started. The drug used was omeprazole belonging to proton pump inhibitors. The drug was administered only to the animals of the Group B and C. It was given orally for the period of 6 weeks. Animals were anesthetized and sacrificed after 6 weeks. Dissection was done to take out the kidneys. They were washed with saline and fixed in 10 % formalin in labeled separate bottles. The kidneys were cut into small pieces which were processed by automatic tissue processer to prepare tissue blocks. These were used to get renal tissue for slide preparation which was then stained with haemotoxylin and eosin to study light the binocular light microscope. The slides were observed for the toxic effects of the acid suppressants.

RESULTS

The renal toxicity was observed in the present study conducted on sixty mice which were divided into three groups having twenty animals in each group. The parameters chosen for the study were qualitative variables so the Persean chi square test was used for the purpose of data analysis. The observations were recorded with the help of MS word and Exel data sheet. The data was entered and analyzed using SPSS (statistical package for social sciences) version 18.0. The interpretation of the p- value was done according to the following criteria.

$p > 0.05$ difference insignificant
$*p < 0.05$ difference significant
$**p < 0.05$ difference considerably significant
$***p < 0.05$ difference highly significant

Group	Therapy	Duration of Therapy
A	Normal saline	6 weeks
B	Drug(20mg)	6 weeks
C	Drug(40mg)	6 weeks

Table-I. Experimental groups distribution

Glomerular Congestion	Group A	Group B	Group C	χ2-test (P-Value)
Absent	20	5	3	0.000
Present	0	15	17	
Total	20	20	20	

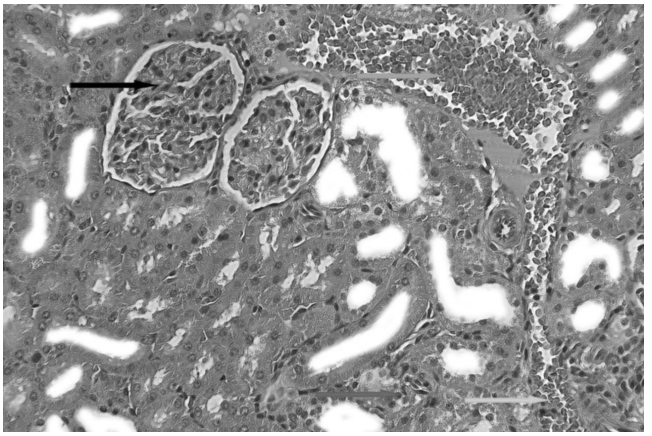
Table-II. Comparison of glomerular congestion

Cellular Infiltrate	Group A	Group B	Group C	χ2-test (P-Value)
Absent	20	3	2	0.000
Present	0	17	18	
Total	20	20	20	

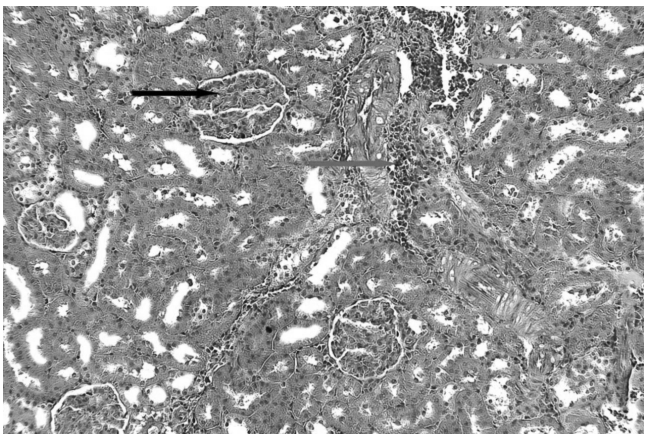
Table-III. Comparison of cellular infiltrate

Photomicrograph of the kidney of group A animal (control group) showing glomerulus (black arrow) and Bowman capsule (sky blue arrow). PCT (blue

arrow) and DCT (green arrow) also visible.



Photomicrograph of the kidney of Group B animal showing congested Glomerulus (Black arrow) and cellular infiltrate (red arrow) H&E x 400 Congested blood vessel (blue arrow) and interstitial hemorrhage (yellow arrow) are also evident.



Photomicrograph of the kidney of animal of Group C showing congested Glomerulus (black arrow) and cellular infiltrate (red arrow) H&E x 400 Interstitial hemorrhage (yellow arrow) is also evident.

DISCUSSION

Stomach is the only organ of the human body that is responsible for the secretion of gastric acid for the sterilization of bacteria contained in the food and digestion of the various nutritional factors. Protective mechanisms prevent the acid induced damage of the gastrointestinal tract. But when acid secretion overcomes these mechanisms, acid related pathological disorders arise. Many inhibitors and neutralizing agents are developed for the treatment of these diseases. Drugs containing aluminum and magnesium have limited effects on acid control so they have been replaced by the H2 Receptor antagonist.[23]

Proton pump inhibitors are widely employed now days for the acid suppression therapy. Associated with their remarkably increased use, adverse effects are also reported including possible allergic reactions, dementia, collagen colitis and nephrotoxicity. Reports have raised the concern about the association between their use and kidney injury.[24] In a prospective study of almost 13 years, the results revealed that Proton pump inhibitors users have 50% increased risk of developing kidney injury than the nonusers.

Mechanism of the development of kidney damage is suspected to be immunological in origin. It is thought to be the result of subclinical interstitial nephritis which progressively leads to the injury of the nephron.[25] In the present study, adverse side effects of the Proton pump inhibitors on the renal tissue were studied. The experimental animals were divided into groups to compare the effects of drug. Acute kidney damage was evident in the animals receiving medicine. The two parameters studied in these animals were the Glomerular congestion and the cellular infiltrate.

Gastric acid secretion is a complex and multifactorial process that is regulated by different stimuli acting on parietal cells. Proton pump inhibitors inhibit the final common pathway for acid secretion. Therefore, they are considered most effective as acid suppression therapy because they directly block the acid pump itself. The results of the study showed that acid suppression therapy consisting of Proton pump inhibitors resulted in the kidney damage by probable binding to the renal tubular basement causing endothelial cell activation by the inflammatory mediators which promotes the leucocyte infiltration. This cellular infiltrate leads to renal toxicity. Literature review reveals other studies also showing the positive relationship between their use and the acute kidney injury.

CONCLUSION

Acid suppression therapy is employed to maintain a level of gastric pH level which prevents the development of gastrointestinal disorders. Among this, Proton pump inhibitors are considered as essential part of the management. The present study was conducted to evaluate the related renal adverse effects of this therapy. Such nephrotoxicity exhibited itself in the form of Glomerular congestion and cellular infiltrate.

It is hoped that the manifestations of this study will create awareness about its clinical use. The prescriber and the user of the drug must be careful about its appropriate indication and dose of the medicine to avoid hazardous effects.

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2	Farwa Naqvi	Abstract, Literature review & methodology.	
3	Nadeem Yaqoob	Performed experiments, Compile & analyze resutls.	
4	Bilal Habib	Typhographical error & brief review.	
5	Nadir Ali Rana	Typhographical error & brief review.	
6	Rao Salman Aziz	Helped in finding resutls.	
7	Amal Shukat	Helped in performing experiments.	
8	Farah Naz Akbar	Helped in performing experiments.	
9	Faiqa Chaudhury	Helped in performing experiments Spelling & grammar mistakes.	
10	Hassan Makhdoom	Helped in performing experiments.	