Original Article

Nephrotoxic Effects of Omeprazole on Renal Vasculature of Albino Wister Rats By Histopathological Study

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ABSTRACT

Objective: To evaluate the nephrotoxicity of increasing doses of omeprazole on the renal blood vessels by the use of an animal model

Study design: Randomized control trial

Materials and Methods: A total of 45 albino wister rats were procured from the Veterinary University Lahore. The animals were randomly divided into three groups, a control group (n=15) that was given distilled water, 2nd group (n=15) was given omeprazole per oral at a dose of 0.3mg/Kg BD and the 3rd group (n=15) was feed with omeprazole at a dose of 0.6 mg/Kg BD. None of the rats died during the study. The animals were sacrificed after 6 weeks of drug administration and the kidneys were dissected out. Histopathology was done to evaluate the slides under the light microscope for glomerular congestion and atrophy, and congestion of blood vessels and haemorrhage in the interstitium. Judgment standards set were either absence or presence of these parameters

Results: None of the rats in the control group (n=15) showed any evidence of injury to the kidneys. While in group 2 (n=15) who were given 0.3mg/Kg 60% (n=9) showed glomerular congestion (P value < 0.0001) while glomerular atrophy was noted in 13.33% (n=2). (P< 0.0001). Group 3 were given 0.6mg/Kg equivalent to dose of 40mg omeprazole BD of 70 Kg of human. This group showed glomerular congestion in 86.67% (n=13) (P< 0.0001) while glomerular atrophy was noted in 26.67% (n=4). (P< 0.0001).Histopathology of the interstitium also showed an increasing tendency of injury as the dose of the omeprazole is increased. In group 2 The injury to interstitium was observed in 33.33 % (n=5)(P= P< 0.0001) while in group 3 it was observed in 53.33% (n= 8)(P= P< 0.0001)

Conclusion: It was observed that omeprazole has toxic effects in the blood vessels of the kidney as shown by the glomerular congestion and atrophy along with the hemorrhage and congestion of the renal interstitium. The incidence of these toxic effects increases as the dose of the drug is increased.

Key Words: Nephrotoxicity, Histopathology, Congestion, Atrophy, Omeprazole,

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INTRODUCTION

Proton pump (H^+/K^+—ATPase) inhibitors belong to the group of the drugs frequently used for the treatment of the disorders related to the gastrointestinal tract such as the peptic ulcer, dyspepsia and gastro esophageal reflux disease. [1]

Proton pump inhibitors are considered as safe medicines but the number of the patients using them is continuously increasing and they are also taking it for the prolonged period of time. This trend has compelled to pay the attention to evaluate the potential hazards associated with this therapy. [2]

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Omeprazole belongs to the group of proton pump inhibitors. It was introduced in 1989 and this made a breakthrough in the management of gastrointestinal disorders. Omeprazole is available as capsule of 20mg and 40mg. Powder form of it is also used for intravenous administration.

Charles S.Wingo [3] stated the observation about location of H/K ATPase pumps in the distal uriniferous tubules of kidney. It was found that these pumps are sensitive to omeprazole.

The renal toxicity of the drugs is frequently reported because of the primary role of the kidneys in the plasma filtration. The exact mechanism is unknown but an immunological basis is suspected for this nephrotoxic effect of the omeprazole. The histological examination of the tissue exposed to the drug shows the presence of inflammatory cells, variation of the normal structure and congestion of the blood vessels.[4,5]

MATERIALS AND METHODS

A total of 45 albino wister rats were procured from the Veterinary University Lahore. The rats were 80 – 100

days old weighting 180 – 240 g. The experimental procedure was carried out according to the international, natural and institutional guidelines for the animal care ethical regulations. [6] All the animals were placed in the cages with bar lids to hold the water bottles and feed. They were kept under constant environmental conditions with temperature of 28.0±2.0ºC and humidity (60±10%) under 12 hour light/dark cycles and well provided with food and water The procedure was carried out in compliance with the ethical consideration. [7, 8]

The animals were randomly divided into three groups **(Table 1).** a control group (n=15) that was given distilled water, 2nd group (n=15) was given omeprazole per oral at a dose of 0.3mg/Kg BD and the 3rd group (n=15) was feed with omeprazole at a dose of 0.6 mg/Kg. BD. None of the rats died during the study. Omeprazole used in this experiment was a product of GETZ Pharmaceuticals with the brand name of RISEK having Omeprazole as 20 mg and 40 mg.

Tissue preparation: The animals were sacrificed after 6 weeks of drug administration. The kidneys were dissected out and fixed in 10 % formalin. Tissue blocks were subjected to slide preparation and stained with hemotoxiline and eosine. [9]

Microscopic examination: Histopathologist who was blinded to the drug administration evaluated the slides under the light microscope for glomerular congestion and atrophy, and congestion of blood vessels and haemorrhage in the interstitium. Judgment standards set were either absence or presence of these parameters

Data entry and analysis: The observations were entered by using the MS Excel data sheet. Statistical analyses were performed using MedCal for Windows, version 12.5.0.0 (MedCal Software, Ostend, Belgium).

RESULTS

The sample size was 45, randomly divided into three groups. None of the rats in the control group (n=15) showed any evidence of injury to the kidneys while in group 2 (n=15) who were given 0.3mg/Kg equivalent to a dose of 20mg omeprazole BD of 70 Kg of human, 60% (n=9) showed glomerular congestion (p= P< 0.0001) while glomerular atrophy was noted in 13.33% (n=2) (p= P< 0.0001). Group 3 was given 0.6mg/Kg equivalent to dose of 40mg omeprazole BD of 70 Kg of human. This group showed glomerular congestion in 86.67% (n=13) (p= P< 0.0001) while glomerular atrophy was noted in 26.67% (n=4) (p= P< 0.0001).

Histopathology of the interstitium also showed an increasing tendency of injury as the dose of the omeprazole is increased. In group 2, the injury to intestiitum was observed in 33.33 % (n=5) (P= P< 0.0001) while in group 3 it was observed in 53.33% (n= 8) (P= P< 0.0001).

Table No.1: Table showing detail of animal groups

Group	Status	Dose	Duration of therapy
1	Control	Normal saline	6 Weeks
2	Treated	20 mg B.D	6 Weeks
3	Treated	40mg B.D	6 Weeks

Table No.2: Comparison of the glomerular congestion in control and treated groups. P value is compared to the control

Groups (n=15) In each group	Glomerular					
	Congestion			Atrophy		
	Absent	Present	χ2-test (p- value)	Absent	Present	χ2-test (p- value)
Group 1 (Control) (normal saline)	15	0		15	0	
Group 2 (20mg BD)	6 (40%)	9 (60%)	P< 0.0001	13 (86.67 %)	2 (13.33 %)	P< 0.0001
Group 3 (40mg BD)	2 (13. 33%)	13 (86. 67%)	P<0.0001	11 (73. 33%)	4 (26. 67%)	P< 0.0001

Table No.3: Comparison of the haemorrhage and congested blood vessels in the interstitium. P value is compared to the control

Groups (n=15) In each group	Interstitium		
	Congestion of blood vessels and hemorrhage		
	Absent	Present	χ2-test (p- value)
Group 1 (Control) (normal saline)	15	0	
Group 2 (20mg BD)	10 (66.67%)	5 (33.33%)	P< 0.0001
Group 3 (40mg BD)	7 (46.67%)	8 (53.33%)	P< 0.0001

DISCUSSION

Proton pump inhibitors are one of the commonly utilized agents for the relief of upper gastrointestinal disorders. They are considered to have a safe profile but their continuous use is associated with the health risks. [10, 11, 12]

In our study we have compared the dose related effects of omeprazole on the renal vasculature by using the albino wister rats as experimental animals. The histological observations of the treated group were compared with the control group. As compared with the control group statistically significant toxic effects evident as glomerular atrophy, glomerular congestion, hemorrhage and congested blood vessels in the interstitium (p=0.0001) are observed in all the rats receiving the omeprazole.

The incidence of the injury also increased when the dose of the omeprazole was increased from 0.3mg/Kg to 0.6mg/Kg (equivalent to 20 mg BD to 40mgBD in a

70 Kg of human) the incidence of glomerular atrophy increased from 13.33% (n=2) to 26.67%(n=2), glomerular congestion from 60% (n=9) to 86.67% (n=13), interstitial hemorrhage and congestion in blood vessels from 33.33%(n=5) to 53.33% (n=8).

Most of the previous studies are in favor of the adverse effects of omeprazole on the renal structure. A study done by the Harmark et al. in 2008 stated the relationship between the kidney damage and the use of omeprazole. [13, 14, 15]

Drug induced renal injury is thought to be responsible for 60- 70 % cases. Medicines induced toxic effects on kidney are frequently encountered. The renal vasculature is exposed to a quarter of resting cardiac output. As a result of it, renal structural cells have to bear significant amount of drug and also its metabolic products which can damage the renal tissue. [16, 17] Proton pump inhibitors are considered as the common causative agents. Another study by the Geevasinga in 2006 concluded that acute renal injury is a serious complication of treatment with the omeprazole which may even end up in renal failure. [18, 19]

Omeprazole acts on the proton pumps located in the distal nephron in addiition to the stomach. It was described by the research that omeprazole selectivity inhibits the H^+-K^+-ATPase and CA; enzymes that are in functional coupling indicating that omeprazole has organ specificity. [20, 21] So an immunological basis is suspected for renal histopathological effects of omeprazole. Drug acting as hapten leads to the development of antibodies. Interstitial inflammation produces the toxic lymphokines that are thought to be involved in the glomerular injury. [22] Histopathological study of the renal tissue showed the presence of cellular and stromal infiltrate. The renal interstitium is more prone to the damage because of the compromised peritubular flow allowing greater exposure time to the medicine.[23] Inflammatory mediators cause the endothelial cell activation leading to vascular permeability.[24]

Congested blood vessels and stromal hemorrhages are observed in the study resulting from weakness of renal vasculature structure by the degenerative effects of omeprazole.[25]

CONCLUSION

The aim of the present study was to evaluate nephrotoxic effects of omeprazole on renal vasculature. The observations showed that omeprazole leads to renal impairment by causing inflammation and congestion of the blood vessels. Therefore, its judicial use should be promoted by the clinicians and the common people to avoid its hazardous effects.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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