Original Article

Renal Histomorphological Effects of Vonoprazan Vs Omeprazole: A Comparative Study in Rats

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Abstract

Objective: This research aimed to assess and compare the nephrotoxicity of omeprazole and vonoprazan on the basis of gross and histomorphological parameters in experimental rats.

Methods: This laboratory-based randomized controlled trial included 60 male Sprague Dawley rats (250 ± 50 g), randomly allocated into three groups: control (Group A), omeprazole-treated (Group B, 20 mg/kg/day), and vonoprazan-treated (Group C, 10 mg/kg/day). Drugs were administered orally for six weeks. Following euthanasia, kidneys were excised, weighed, and prepared for microscopic analysis using hematoxylin and eosin (H&E) and Masson's trichrome stains. Data analysis was done using SPSS 26, with statistical significance set at $p < 0.05$.

Results: Omeprazole-treated rats exhibited significant reductions in glomerular diameter (23.5 ± 1.9 µm vs. 37.9 ± 1.3 µm in controls, $p < 0.000$), kidney weight (0.92 ± 0.12 g vs. 1.39 ± 0.09 g, $p < 0.000$), and relative tissue body weight index (RTBWI) (0.37 ± 0.06 vs. 0.50 ± 0.04, $p < 0.000$). The vonoprazan-treated rats showed relatively normal renal morphology with fewer histological changes and non-significant changes in renal parameters as compared to controls.

Conclusion: Omeprazole-induced nephrotoxicity was manifested as histopathological injury and deranged renal function parameters. Vonoprazan, on the other hand, showed a comparatively safer renal profile and indicated it to be an ideal nephroprotective drug alternative to proton pump inhibitors. Further studies are required to validate such findings and elucidate the mechanisms behind them.

Keywords: Chronic Kidney Disease, Nephrotoxicity, Proton Pump Inhibitors.

Contributions:
KH, AQ, - Conception, Design
KH, AQ, MMK, NW, HR, MA - Acquisition, Analysis, Interpretation
KH, NW - Drafting
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Introduction

Gastrointestinal acid-related disorders respond to treatment with widely used proton pump inhibitors, particularly omeprazole. Steady drug use has shown associations with kidney toxicity, which might cause either acute interstitial nephritis (AIN) or chronic kidney disease (CKD).[1] Oxidative stress, combined with fibrosis together with immune-mediated injury produce renal function impairment through pathophysiological mechanisms.[2]

PPIs mainly transform in the liver by the cytochrome P450 system through the action of the isozyme CYP2C19. Variations of the CYP2C19 gene sequence affect drug metabolic pathways, which either decrease treatment effectiveness or produce toxic buildup of active drug compounds.[3] Omeprazole metabolites that accumulate because of frequent exposure trigger AIN development through hypersensitivity as the initial step that leads to renal fibrosis.[4]

The toxic effect of omeprazole on kidney tubular cells manifests as mitochondrial cell damage, together with accelerated lipid breakdown. The accumulated reactive oxygen species (ROS) generate oxidative stress that triggers damage to renal epithelial cells and breaks cellular equilibrium.[5]

A newer alternative is Vonoprazan, a P-CAB (potassium-competitive acid blocker) lately because of the reversible binding to the H+/K+-ATPase with more stable inhibition of gastric acid.[6] That is, the vonoprazan does not need to be activated under acidic conditions, is stable in plasma, and thus has predictable pharmacokinetics and generation of nephrotoxic metabolites.[7] The clearance rate from parietal cells is slow; hence, the drug is more stable. For these reasons, it is superior to omeprazole and other PPIs with respect to its gastric protective effect.[8] Vonoprazan's good safety profile has been demonstrated in clinical studies on gastric and duodenal ulcers, reflux esophagitis, NSAID-associated ulcers and H. pylori eradication.[6]

Animal studies with vonoprazan did not demonstrate renal histomorphological damage comparable to that of omeprazole, hence providing a need for a study in this area.

According to some animal research, vonoprazan has demonstrated reduced nephrotoxicity and less reduction of glomerular filtration rate (GFR) as compared to other PPIs.[7] Other researchers found no association between the use of vonoprazan and the onset of nephrotoxicity.[9] However, some Japanese researchers found out the development of tubulointerstitial nephritis with vonoprazan use, similar to that caused by other PPIs and emphasized the monitoring of renal functions during the usage of this drug.[10] The studies highlighted the need for further investigation to validate the

development of adverse effects of vonoprazan and to dig into the underlying cause and mechanisms responsible for their development.[11] The less established adverse effects profile of vonoprazan as compared to omeprazole has led to the conduct of this study, so that the toxicity of omeprazole can be reduced by replacing it with vonoprazan.

Materials And Methods

This laboratory-based randomized control trial involved 60 male Sprague Dawley rats (250 ± 50 g). The sample was obtained through a purposive sampling technique. The rats were housed under controlled temperature and humidity conditions, with free access to standard laboratory chow and water. The study was conducted from August 2024- February 2025 after ethical approval was obtained from the Army Medical College, Rawalpindi. Healthy adult male rats 3-4 months of age weighing 250±50 grams of weight were included in the study. Rats having any gross abnormality were excluded.

Rats were allocated into three distinct groups of twenty each through a randomized process. The randomization of the animals was executed using a computer-generated random order system.

The experimental groups were as follows:

- Group A (Control): Received distilled water orally for six weeks.
- Group B (Omeprazole-treated): Administered omeprazole (20 mg/kg/day) dissolved in distilled water. The drug was given in a therapeutic clinical dose based on existing animal studies.[12]
- Group C (Vonoprazan-treated): Administered vonoprazan (10 mg/kg/day) dissolved in distilled water. The dose of vonoprazan was therapeutic, and derived from the other pharmacokinetic studies of this drug done on animals.[13]

The method of dose calculation has been given in Appendix I.

Rats were euthanized by keeping them in glass containers filled with diethyl ether overdose. The abdominal cavity was accessed by a vertical incision made along the midline. Following the removal of the surrounding adipose and connective tissues, the kidneys were exposed and removed. They were weighed carefully using a digital weighing balance.

Kidneys were dissected following euthanasia and subsequently fixed in 10% formalin. Sections were stained with H&E for histopathological assessment. Glomerular diameters were measured using the line tool of ImageJ software.

An Olympus® digital camera with 10 megapixels, model Stylus 1010, was used through the eyepiece of a light microscope, Olympus CX21FSI, having a tube length of 160 mm. The photos were corrected, as necessary, for contrast, brightness, sharpness, and color balance. They were labelled using PhotoScape software. Data were analyzed using SPSS 26. One-way ANOVA with post hoc Tukey's test was applied for intergroup comparisons, with $p < 0.05$ considered significant.

i. Weight of the Animals

Body weights of all rats were measured at the commencement of the study and just before dissection (end of experimental period) using a digital balance (0-5 kg capacity). The mean weight gain of animals in all groups was obtained and compared.

ii. Weight of the Kidneys

Kidneys were weighed on a digital weighing balance.

iii. Relative Tissue Weight Index (RTBWI)

Rats of various sizes had their kidney weights standardized by applying the following formula to determine the Relative Tissue Body Weight Index.[14]

$$\text{RTBWI} = \frac{\text{Kidney weight (grams)}}{\text{Body weight (grams)}} \times 100$$

iv. Transvertical Diameter of Glomerulus

The glomeruli were chosen at random from three distinct areas on a single slide for each specimen, observed under a magnification of 40X. The measurements of both the transverse and vertical diameters of each glomerulus were taken using the line tool of ImageJ software. The average of both diameters was determined as the transverse diameter.[15] Three measurements were taken, and then their mean was taken as the observed diameter of the glomeruli for the particular specimen.

Results

i. Weight of the Animals

All of the animals' body weights were noted at the start and the end of the experiment. The mean initial weights of groups A, B and C were 242.98 ± 13.68, 227.2 ± 19.7 and 229.9 ± 14.8 grams, respectively. At the end of the study, the mean final weights were increased to the values of 268.2 ± 13.98, 248.5 ± 19.9. and 267.7 ± 14.3 grams respectively. While there was no significant difference in mean weight gain between groups A and C (P-value = 0.507), statistically significant disparity was found between control group A and experimental group B (P-value = 0.000) upon intergroup comparison.

Table 1: Intergroup comparison of mean weight gain between control group A and experimental groups B & C.

Parameter	Groups	Mean ± SD	Statistical Significance		
			Group A/B	Group A/C	Group B/C
Mean weight gain (grams)	A	38.9 ± 2.2	0.000	0.507	0.000
	B	21.3 ± 1.8			
	C	± 4.5			

ii. Weight of the kidneys

The mean weight of the kidneys of the right side of all the groups was recorded. The mean kidney weight of group A was 1.39 ± 0.09, of group B was 0.92 ± 0.12, and of group C was 1.05 ± 0.14. Upon intergroup comparison, statistically significant difference was recorded between control group A and experimental groups B (p-value=0.000) and C (p-value=0.004).

Table 1: Intergroup comparison of mean weight of rat kidneys between control group A and experimental groups B & C

Parameter	Groups	Mean ± SD	Statistical Significance		
			Group A/B	Group A/C	Group B/C
Mean kidney weights (grams)	A	1.39 ± 0.09	0.000	0.000	0.004
	B	0.92 ± 0.12			
	C	1.05 ± 0.14			

iii. Relative tissue body weight index (RTBWI)

The RTBWI for the omeprazole group was 0.37 ± 0.06, the vonoprazan group was 0.39 ± 0.06, and the control group was 0.50 ± 0.04. ANOVA and the post-hoc Tukey's test revealed highly significant differences (p=0.000) when experimental groups B and C were compared to control group A. The difference between experimental groups B and C was not significant (P-value = 0.535).

Table 3: Intergroup comparison of mean Relative tissue body weight index of control group A and experimental groups B & C.

Parameter	Groups	Mean ± SD	Statistical Significance		
			Group A/B	Group A/C	Group B/C
Relative tissue body weight index	A	0.50 ± 0.04	0.001	0.001	0.535
	B	0.37 ± 0.06			
	C	0.39 ± 0.06			

iv. Transvertical diameter of glomerulus

Mean transvertical diameter (TVD) of glomeruli of the control group was measured to be 37.93 ± 1.33 µm, that of the omeprazole group was 23.5 ± 1.90 µm, and that of vonoprazan group was 36.4 ± 1.19 µm (Figure no. 1). Upon intergroup comparison, TVDs of glomeruli of the control and omeprazole groups had p-value of 0.000, which indicates high statistical significance. In contrast, the TVDs of the vonoprazan group did not differ statistically from the control group (P-value 0.008), but they did differ significantly from the omeprazole group (P-value 0.000) (Table 4).

Table 4: Intergroup comparison of Mean transvertical diameters between control group A and experimental groups B and C.

Parameter	Groups	Mean ± SD	Statistical Significance (P-Value)		
			Group A/B	Group A/C	Group B/C
Transverse diameter of glomerulus (µm)	A	37.9 ± 1.33	0.000	0.007	0.000
	B	23.5 ± 1.90			
	C	36.4 ± 1.19			

The current study investigated the histomorphological effects of administration of the Proton Pump Inhibitor, omeprazole and the Potassium competitive acid blocker, vonoprazan, on the rat kidneys. The nephrotoxic effects were assessed on the renal corpuscle through gross and histological analyses. The results demonstrated marked reduction in glomerular diameters along with changes in body weight and RTBWI in the omeprazole-treated group. The vonoprazan group exhibited minimal to no such changes, similar to the control group.

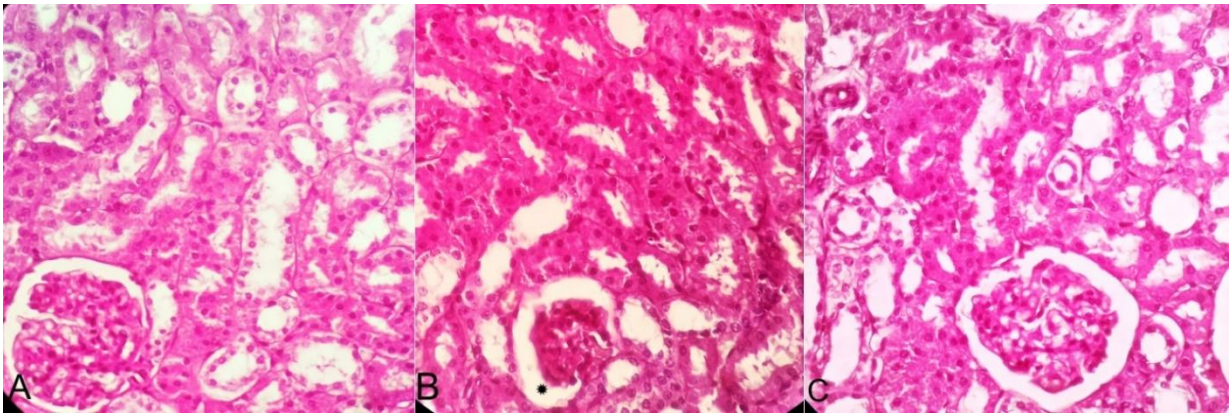

Figure no 1: H&E stained photomicrograph showing shrunken glomerulus in B and normal glomeruli in A & C. Asterisk shows widening of Bowman's space in B. Magnification: 40X

Discussion

Omeprazole-induced nephrotoxicity is linked to AIN, oxidative stress, and fibrogenesis.[16]

The analysis of gross parameters revealed significant differences in kidney weight and Relative Tissue Body Weight Index (RTBWI) between the control and experimental groups. Specifically, the kidney weight of rats given omeprazole (Group B) exhibited a marked decrease when compared to the control group (Group A) ($p<0.000$), which implies renal atrophy. Similar findings were noted in a study, where extended exposure to PPIs led to renal parenchymal shrinkage and fibrosis.[17] Vonoprazan-treated group (Group C) showed less weight reduction in relation to the control group ($p=0.004$), indicating reduced structural changes compared to those of omeprazole. However, these variations highlight the complexities of drug impact on renal health; this warrants further investigation. In comparison to the control and vonoprazan groups, the omeprazole group also showed a significant decrease in RTBWI. This aligns with findings of a meta-analysis of various studies, which demonstrated that chronic administration of PPIs leads to reductions in organ-to-body weight ratios due to interstitial fibrosis and nephron loss.[18] However, the vonoprazan-treated group exhibited a relatively preserved RTBWI, indicating that vonoprazan may exert comparatively less structural damage on the kidney.

The outcome of this study revealed a significant decrease in glomerular transvertical diameters in the omeprazole-treated group, but a less significant difference in diameters of the vonoprazan-treated group. Research demonstrated widening of Bowman space, shrunken glomeruli, and tubular cell congestion in long-term PPI-treated male rats.[19] A study carried out on male rats to visualize the histomorphological changes produced in kidneys in response to omeprazole treatment revealed glomerular changes consisting of shrunken glomeruli and hyper-cellularity in the Bowman's space, similar to the results of the present study.[20] Possible mechanisms responsible for renal damage include endothelial dysfunction, oxidative stress and vascular senescence from long-term PPI use that damages endothelial function and accelerates endothelial senescence. Also, because magnesium deficiency raises the risk of kidney disease through oxidative stress, inflammation, and endothelial cell dysfunction, the production of hypomagnesemia by PPIs can support the association between PPI usage and CKD.[21] According to research on omeprazole toxicity, it caused cell death in a dose-dependent manner across human and murine proximal tubular cell lines. The cell death exhibited necrotic characteristics, such as annexin V/7-AAD positivity, LDH release, cytoplasmic vacuolization, and abnormal chromatin condensation. It also triggered strong oxidative stress affecting mitochondria and lysosomes. Cell death was also worsened by the production of iron overload.[22] A histomorphological study on rat kidneys conducted in Egypt revealed renal tubular distortion and disruption of basement membranes of tubules and glomerular capillaries.[23]

In contrast, vonoprazan exhibited a relatively preserved renal histology, with minor glomerular changes, indicating lower nephrotoxicity. Unlike PPIs, vonoprazan competitively inhibits H+/K+-ATPase without forming covalent bonds, reducing potential antigenic stimulation.[24] Vonoprazan undergoes hepatic metabolism mainly via CYP3A4, with minimal involvement of CYP2C19, leading to fewer nephrotoxic metabolites (Miao et al., 2023). These findings align with studies suggesting vonoprazan's superior safety profile and lesser adverse effects.[7]

Conclusions

This study highlights the nephrotoxic potential of chronic omeprazole use, evidenced by significant reductions in glomerular diameters, kidney weight, and RTBWI. The findings align with previous studies demonstrating omeprazole-induced acute interstitial nephritis and oxidative stress-related renal injury. Conversely, vonoprazan exhibited a relatively preserved renal

structure with minimal renal structural changes, suggesting a lower risk of nephrotoxicity. These results suggest that vonoprazan may be a safer replacement for PPIs in patients at risk of kidney dysfunction. To validate these results and investigate the underlying processes of renal injury linked to acid-suppressive treatments, more clinical and long-term animal research is needed.

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