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ORIGINAL ARTICLE

Physiological and Histological Effects of Linezolid on the Kidney and Stomach of Rats

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ABSTRACT

Linezolid is an oxazolidinone antibacterial agent for the treatment of resistant gram-positive infections. However, prolonged or high exposure to linezolid may cause mitochondrial toxicity and organ injury. This exploratory rat study aimed to assess biochemical and histological findings following exposure to treatment-dose and toxic-dose linezolid with emphasis on kidney and stomach tissues. The study involved 18 male rats, divided into 3 groups of 6 rats each. Group 1 was the treatment-dose linezolid group. Group 2 was the toxic-dose linezolid group. the remaining rats were used as a control group. The toxic-dose was 100 mg/kg/day for 14 days orally. Six animals were used as a control. Blood urea, serum creatinine, AST/SGOT, ALT/SGPT and alkaline phosphatase were presented as mean ± SD and hematoxylin-and-eosin-stained renal and gastric sections were interpreted descriptively. The treatment-dose group showed blood urea, serum creatinine, AST/SGOT, ALT/SGPT, and alkaline phosphatase values of 38.91 ± 4.15 mg/dL, 1.12 ± 0.18 mg/dL, 35.83 ± 12.16 U/L, 34.99 ± 10.87 U/L, and 59.83 ± 12.26 U/L, respectively. The toxic-dose group showed corresponding values of 30.74 ± 7.35 mg/dL, 1.05 ± 0.33 mg/dL, 34.09 ± 8.78 U/L, 39.81 ± 5.92 U/L, and 51.09 ± 10.73 U/L. Gastric sections showed mucosal necrosis, epithelial sloughing, glandular distortion, inflammatory infiltration, edema, and vascular congestion. Renal sections showed tubular degeneration, tubular dilatation, epithelial desquamation, interstitial inflammation, vascular congestion, and glomerular alterations. Histology evidence showed a significant damage in renal parameters and histopathological slides represented by gastric and renal tissue injury in the examined linezolid exposed sections of the current exploratory rat study and the damages were dose dependent as all of the damages were increased in the toxic dose however physiological parameters did show a toxic effect but these effects were not a dose dependent.

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1- INTRODUCTION

Linezolid is the first clinically successful oxazolidinone antibacterial agent and is used mainly for serious infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci [1, 2]. Its antibacterial activity is mediated through inhibition of bacterial protein synthesis by binding to the 23S ribosomal RNA of the 50S ribosomal subunit and preventing formation of the functional 70S initiation complex [3]. The drug has excellent oral bioavailability and clinically useful tissue penetration, which explain its wide therapeutic use in difficult infections [4, 5, 6]. Despite its clinical usefulness, linezolid is associated with important adverse effects. The best-recognized toxicities include thrombocytopenia, anemia, leukopenia, peripheral and optic neuropathy, serotonin-related reactions, gastrointestinal intolerance, and lactic acidosis [7-8]. These adverse outcomes are especially important during prolonged treatment or high systemic exposure. Mechanistically, linezolid toxicity is commonly linked to inhibition of mitochondrial protein synthesis, because mitochondrial ribosomes retain structural similarities to bacterial ribosomes [9,10]. Mitochondrial dysfunction can impair oxidative phosphorylation, increase oxidative stress, and contribute to cellular injury in energy-dependent tissues. Experimental studies in rats support the use of linezolid as a model for drug-related hematological, hepatic, and renal toxicity. Oral administration of linezolid at 100 and 250 mg/kg/day for 15 days produced dose-dependent reductions in blood cell counts and antioxidant enzyme activity, with increased lipid peroxidation and nitric oxide production [11]. Previous studies about hepato-renal toxicity model used linezolid at 100 mg/kg/day by oral gavage for 14 days and reported increased serum creatinine, urea, liver enzymes, oxidative stress, inflammatory mediators, apoptosis-related changes, and histopathological tissue injury [12-16]. Comparative nephrotoxicity experiments have also documented linezolid-associated renal biochemical and histological alterations, although often less severe than vancomycin-induced renal damage [17-20]. The present study evaluated the physiological and histological effects of linezolid on kidney and stomach.

2- MATERIALS AND METHODS

2.1 Study design and animals

The experimental study involved 18 male rats 8–10 weeks of age and weighing 180–220 g obtained frome the veterinary collage – university of Tikrit and divided into 3 groups of 6 rats each, exposed to linezolid. Group 1 was the treatment-dose linezolid group. Group 2 was the toxic-dose linezolid group. the remaining rats were used as a control group. Housing conditions, acclimatization period, diet, environmental temperature, humidity and light-dark cycle were considered according to the ARRIVE 2.0 guidelines for transparency in animal research [21].

2.2 Ethical approval

All procedures were approved by the veterinary collage institutional committee/ university of Tikrit according to [22].

2.3 Linezolid administration

Group 1 received the treatment-dose linezolid regimen, 50 mg/kg/day orally for 14 consecutive days. Group 2 received linezolid orally at a toxic dose of 100 mg/kg/day for 14 consecutive days [14].

2.4 Blood collection and biochemical assays

At the end of the experiment blood samples were collected for biochemical analysis. The biochemical parameters were blood urea, serum creatinine. AST/SGOT, ALT/SGPT and alkaline phosphatase were measured to assess possible extra-renal/hepatic effects of linezolid.

2.5 Histopathological processing

Kidney and stomach tissues were examined histologically using hematoxylin and eosin-stained sections. All tissue samples were fixed in 10% neutral formaldehyde solution (formalin) at least for 24 hr. After being processed (dehydration, waxing, 4–5 µm sections) and stained with Hematoxylin and Eosin (H&E). A semi quantitative scoring system was used to improve the reproducibility of histopathological interpretation [23-25].

2.6 Statistical analysis

Data are expressed as mean ± standard deviation. SPSS was used for statistical analysis of the treatment groups. Data were analyzed using one-way ANOVA followed by Tukey's multiple-comparison test. Histological scores and non-normally distributed or ordinal data were analysed with Kruskal–Wallis test with Dunn’s post hoc test [26, 27].

3- RESULTS AND DISCUSSION

Individual biochemical values are presented in Table 1, The treatment-dose group showed mean blood urea and serum creatinine values of 38.91 ± 4.15 mg/dL and 1.12 ± 0.18 mg/dL, respectively. In the toxic-dose group, the corresponding values were 30.74 ± 7.35 mg/dL and 1.05 ± 0.33 mg/dL. Mean AST/SGOT, ALT/SGPT, and alkaline phosphatase were 35.83 ± 12.16 U/L, 34.99 ± 10.87 U/L, and 59.83 ± 12.26 U/L in the treatment-dose group, and 34.09 ± 8.78 U/L, 39.81 ± 5.92 U/L, and 51.09 ± 10.73 U/L in the toxic-dose group.

Table (1): biochemical parameters in the two linezolid-exposed groups

Parameter	Unit	Control (n=6)	Treatment-dose linezolid (n=6)	Toxic-dose linezolid (n=6)	ANOVA p-value
Blood urea	mg/dL	29.00 ± 2.35[a]	38.91 ± 4.15[b]	33.74 ± 7.35[c]	0.009
Serum creatinine	mg/dL	0.85 ± 0.15[a]	1.12 ± 0.18[c]	1.05 ± 0.33[b]	0.005
AST/SGOT	U/L	31.00 ± 3.21[a]	35.83 ± 12.16[b]	34.09 ± 8.78[b]	0.040
ALT/SGPT	U/L	33.00 ± 5.12[a]	34.99 ± 10.87[a]	39.81 ± 5.92[b]	0.032
Alkaline phosphatase	U/L	45.00 ± 6.21[a]	59.83 ± 12.26[b]	51.09 ± 10.73[c]	0.045

Footnote: Values are presented as mean ± SD. Data were analyzed using one-way ANOVA followed by Tukey's multiple-comparison test. Different superscript letters within the same row indicate statistically significant differences ($p \leq 0.05$), whereas means sharing the same superscript letter are not significantly different.

The available biochemical data did not show a consistent numerical worsening in the toxic-dose group compared with the treatment-dose group. In fact, blood urea, serum creatinine, AST/SGOT, and alkaline phosphatase means were numerically lower in the toxic-dose group, whereas ALT/SGPT was numerically higher. These findings were in consistent with other studies that investigated the effect of the studied drug on the same parameters [13-20]. Group 1 section had moderate to marked gastric mucosal injury. In some areas the glands were irregular and distorted and had lost their normal organization. The lamina propria was expanded by oedema and infiltration of inflammatory cells. Degenerative epithelial changes were characterized by cellular swelling, nuclear condensation and partial epithelial desquamation. There were also congested vascular spaces and focal hemorrhagic changes. The architecture was more recognizable compared to Stomach 2 but the section still showed clear gastric epithelial degeneration, inflammation and mucosal structural damage. Histological examination of gastric images demonstrated mucosal injury of varying degree. The group 2 section showed severe mucosal destruction with almost total loss of normal glandular architecture. Tissue showed widespread epithelial desquamation, mucosal necrosis, disruption of lamina propria, necrotic cellular debris, intensely basophilic fragmented material, marked infiltration of inflammatory cells, stromal disorganization, hemorrhagic or exudative alterations. These results indicate advanced gastric mucosal injury with severe necrotic and inflammatory alteration (Figure 1 group 1).

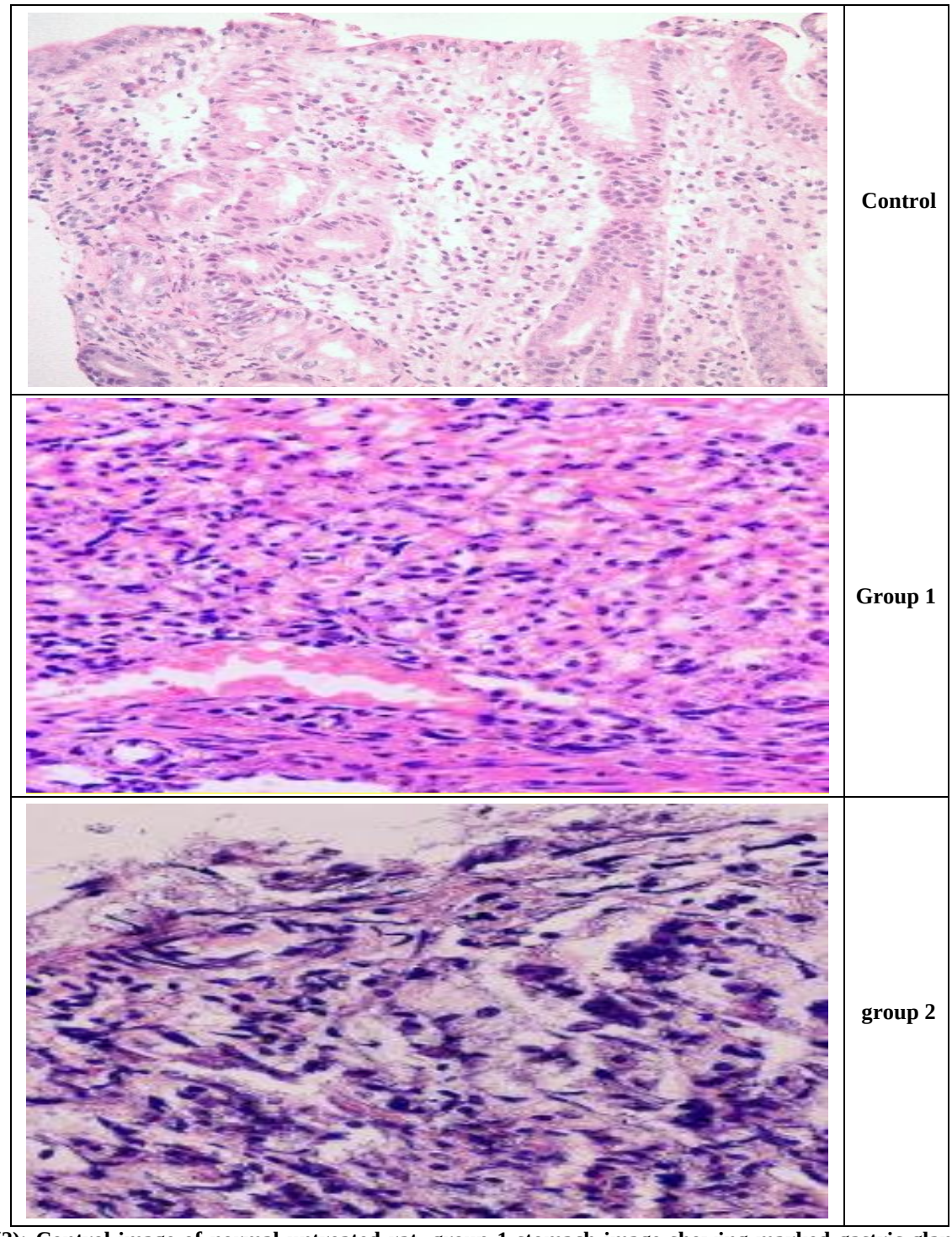


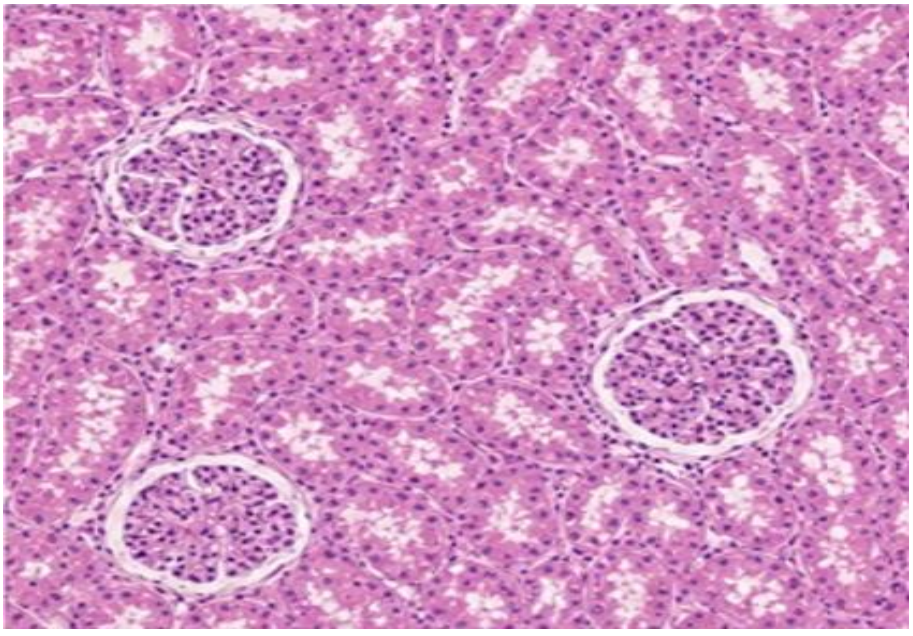
Fig (2): Control image of normal untreated rat. group 1 stomach image showing marked gastric glandular distortion, epithelial degeneration, focal desquamation, lamina propria edema, vascular congestion, necrosis, and inflammatory cell infiltration. group 2 stomach image showing severe disruption of gastric mucosal architecture, epithelial degeneration, necrosis, inflammatory cellular infiltration, and cellular disorganization. H&E-stained sections; 400X.

Table (2): Semi-quantitative stomach histopathological scoring

Group	Glandular distortion	Epithelial degeneration,	Focal desquamation	Edema	Inflammatory cell infiltration	Necrosis	Total injury score
Normal control	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–1)[a]
Treatment dose	2 (2–3)[c]	2 (2–3)[c]	2 (1–2)[c]	2 (1–3)[c]	2 (2–3)[c]	2 (1–2)[c]	12 (10–13)[b]
Toxic dose	4 (3–4)[b]	4 (3–4)[b]	3 (3–4)[b]	3 (3–4)[b]	4 (3–4)[b]	3 (3–4)[b]	21 (18–23)[c]

Table annotation. Values are presented as median (interquartile range). Stomach histopathological lesions were scored semi-quantitatively on a 0–4 ordinal scale: 0 = absent/normal, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. Groups sharing at least one superscript letter are not significantly different.

The section labeled Kidney of group 1 showed mild-to-moderate renal cortical injury. The glomerular tuft was largely preserved, although mild congestion and widening of Bowman's space were visible. Tubular epithelial cells displayed cloudy swelling and vacuolar degeneration, with focal tubular dilatation and partial narrowing or irregularity of tubular lumina. Mild interstitial congestion and scattered inflammatory cells were present. Compared with Kidney 2, the renal architecture was relatively better preserved, suggesting less severe renal damage dominated mainly by tubular epithelial degeneration rather than extensive necrosis. Renal cortical images also showed tissue injury of variable severity. The area designated group 2 kidney displayed severe nephrotoxic injury affecting tubular, glomerular, vascular, and interstitial regions. Several renal tubules were dilated and irregular in shape with epithelial swelling, vacuolar degeneration, rarefaction of cytoplasm, partial loss of tubular epithelial lining, focal necrosis of epithelium and desquamated cells in tubular lumina. The interstitium showed an inflammatory cell infiltrate and vascular congestion. Glomerular changes included widening of Bowman's space in some areas, and glomerular tuft congestion or shrinkage. These results are consistent with significant tubular degeneration of the renal tubules associated with glomerular and interstitial injury (Figure 2).


control

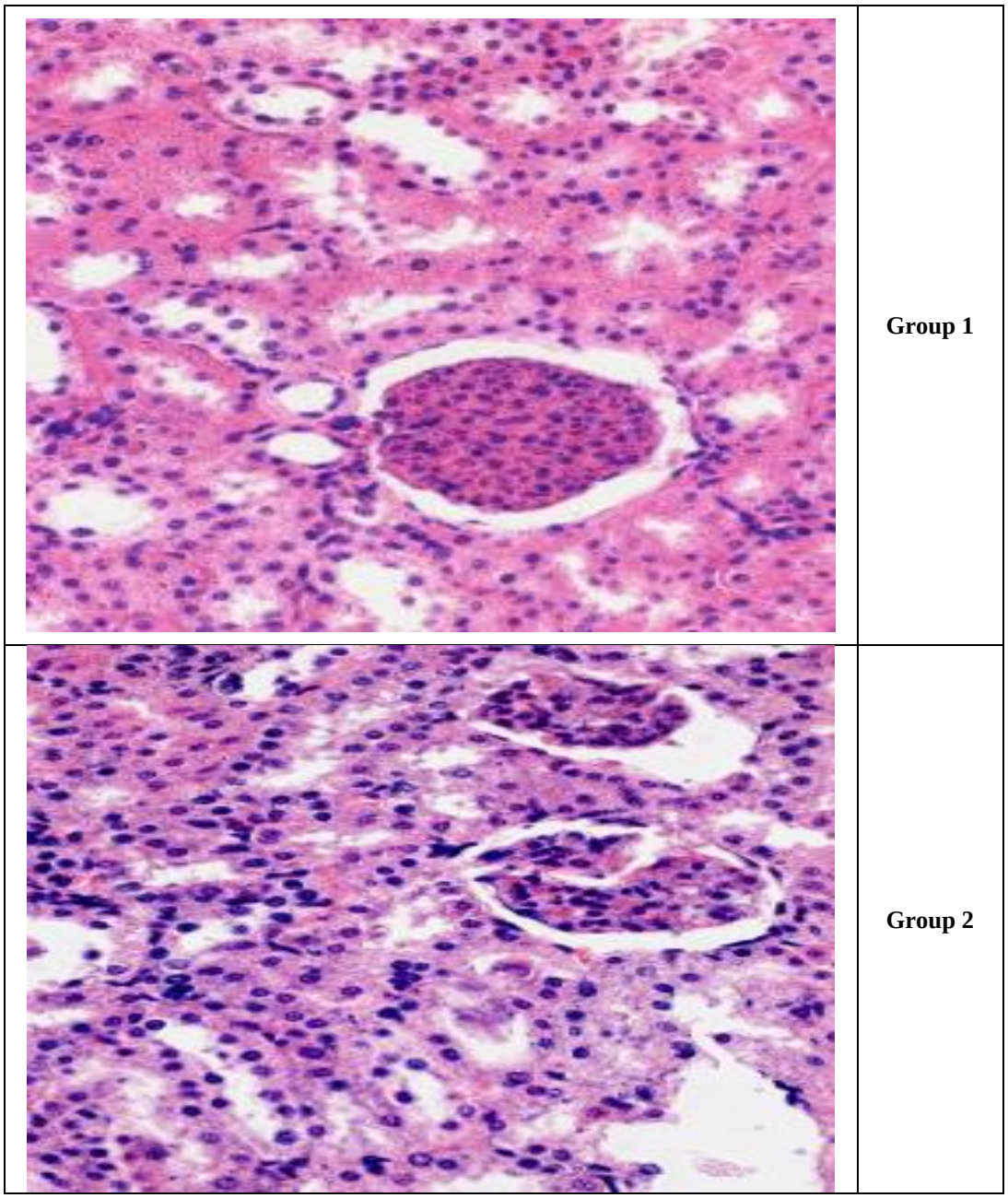


Fig (2): control kidney image of untreated ret. group 1 Kidney image showing relatively preserved renal architecture with mild-to-moderate tubular epithelial degeneration, focal tubular dilatation, glomerular congestion, mild widening of Bowman's space, and limited interstitial inflammatory infiltration. Group 2 Kidney image showing prominent tubular epithelial degeneration, tubular dilatation, epithelial desquamation, focal necrotic change, interstitial inflammatory infiltration, vascular congestion, and glomerular alteration with widening of Bowman's space. H&E-stained sections. 400X.

Table (3): semi-quantitative renal histopathological scoring

Group	Epithelial degeneration / desquamation	Tubular dilation	Congestion	epithelial desquamation	Inflammatory cell infiltration	Glomerular / Bowman's space alteration	Total renal injury score
Normal control	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–0)[a]	0 (0–1)[a]
Treatment dose	2 (2–3)[c]	2 (2–3)[c]	2 (1–2)[c]	2 (1–3)[c]	2 (2–3)[c]	1 (1–2)[c]	11 (9–13)[c]
Toxic dose	4 (3–4)[b]	4 (3–4)[b]	2 (1–2)[c]	2 (1-2)[c]	3 (2–4)[b]	2 (1–3)[b]	17 (16–18)[b]

Table annotation: Values are presented as median (interquartile range). Renal histopathological lesions were scored semi-quantitatively on a 0–4 ordinal scale: 0 = absent/normal, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. Groups sharing at least one superscript letter are not significantly different.

Biochemical and histopathological results indicated variable sensitivities to linezolid-induced renal injury. No consistent dose-response relation was seen for the traditional markers of renal function, particularly serum urea and creatinine. Conversely, renal histopathology showed a marked and progressive increase in structural injury with the total renal injury score increasing from 0 in controls to 11 in the treatment-dose group and 17 in the toxic-dose group. The increasingly severe tubular epithelial degeneration, tubular dilation, inflammatory infiltration and glomerular/Bowman's space alterations with increasing linezolid exposure give more solid evidence of a dose-dependent renal toxic effect. The lack of a parallel biochemical response may be explained by the poor sensitivity of traditional circulating markers of renal function to early or moderate structural renal injury [21,22]. Serum urea and creatinine are functional markers that may be relatively insensitive in early, focal or heterogeneous renal injury. Histological lesions may appear before large systemic changes in serum markers, particularly in small exploratory studies. Conversely, preanalytical variability, hydration status, timing of sampling, assay variation, and individual biological variation can influence biochemical values. Therefore, the most scientifically balanced interpretation is that histology demonstrates morphological tissue injury in the examined slides, whereas the biochemical data are insufficient to establish a clear dose-related functional deterioration [28]. Mechanistically, linezolid toxicity is biologically plausible. In bacteria, linezolid inhibits protein synthesis at the ribosomal initiation stage. In mammalian cells, adverse effects are linked to off-target inhibition of mitochondrial ribosomes, leading to impaired mitochondrial protein synthesis, reduced respiratory chain function, oxidative stress, and energy imbalance [29]. Experimental studies report oxidative stress, reduced antioxidant defense, increased inflammatory mediators, and apoptosis-related alterations after repeated linezolid exposure [30].

4- CONCLUSION

In conclusion, Histology evidence showed a significant damage in renal and these damages were dose dependent as all of the damages appeared in the histopathological slides as all of the damages were increased in the toxic dose group, however the studied biochemical parameters did show a toxic effect of the Linezolid but the effect was not a dose dependent.

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