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ORIGINAL ARTICLE

# Blood chemical changes and renal histological alterations induced by gentamicin in rats

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*Rattus norvegicus*

**Abstract** Gentamicin is an effective widely used antibiotic, but the risk of nephrotoxicity and oxidative damage limit its long-term use. Hence, the current study aims to elucidate such hazardous effects. To achieve the study aim male Wistar albino rats (*Rattus norvegicus*) were exposed to gentamicin to investigate the resultant blood chemical changes and renal histological alterations. In comparison with control rats, gentamicin produced outstanding tubular, glomerular and interstitial alterations that included degeneration, necrosis, cytolysis and cortical tubular desquamation together with mesangial hypercellularity, endothelial cell proliferation and blood capillary congestion. Compared with control animals significant blood chemical changes ($P < 0.05$) including free radicals, ALT, AST, ALP, serum creatinine and serum urea were recorded in gentamicin-injected animals. The findings revealed that exposure to gentamicin can induce significant histological alterations in the kidney as well as remarkable blood chemical changes that might indicate marked renal failure.


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## 1. Introduction

The kidney is a vital organ in health and disease. Many environmental contaminants and chemical variables, including drugs, alter the functions of the kidney (Mahmood and Waters, 1994; Begg and Barclay, 1995).

Gentamicin (GM) is an effective aminoglycoside antibiotic that is still widely used against serious and life-threatening infections by Gram-positive and Gram-negative aerobic bacteria, but nephrotoxicity and oxidative damage limits its long-term clinical use (Whelton and Neu, 1982; Abdel-Naim

et al., 1999; Hansen et al., 2001; Al-Majed et al., 2002; Abo El-Sooud, 2003; Ali et al., 2005; Dhanarajan et al., 2006; Ekor et al., 2006; Kuhad et al., 2006; Nagai et al., 2006; Ali et al., 2008; Priyamvada et al., 2008; Khan et al., 2009; Abdel-Raheem et al., 2009; Ali et al., 2011). Gentamicin-induced nephrotoxicity was reported in previous studies (Erdem et al., 2000; Karahan et al., 2005; Buba et al., 2011; Chaware et al., 2011; Kore et al., 2011; Sharma et al., 2011). Other studies have shown that gentamicin also causes ototoxicity, skin rash, neuromuscular blockage, genotoxicity, hepatotoxicity, oxidative damage, structural chromosomal aberrations and fragmentation (Mingeot-Leclercq and Tulkens, 1999; Chambers, 2001; Schulze and Wollina, 2003; Yasin et al., 2003; Amici et al., 2005; Parlakpinar et al., 2005; Sharifzadeh et al., 2005; Hong et al., 2006; El-Ashmawy et al., 2006; AlKahtani et al., 2009; Kandeel et al., 2011).

Studies on histological alterations in renal tissues due to gentamicin are limited and have not been fully identified. With this objective, a detailed histological study was undertaken using the kidneys of Wistar albino rats killed at one-week intervals up to four consecutive weeks after gentamicin treatment. Additionally, blood chemical investigation was conducted for more elucidation of the effect of tissue damage which could be provoked by gentamicin.

## 2. Materials and methods

All of the experimental procedures were conducted in the Histology and Cell Biology Lab., of the King Saud University, Saudi Arabia, between 2010 and 2011.

Thirty-six male Wistar albino rats (*Rattus norvegicus*) of the same age weighing 220–250 g were obtained from the Animal House of King Saud University, Riyadh, Kingdom of Saudi Arabia. Animals were randomly assigned to three groups of 12 rats each and housed in metabolic cages. Following a period of stabilization (7 days), gentamicin in the form of gentamicin sulfate (gentamicin injection, 40 mg/ml, Sandoz, Switzerland) was administered intramuscularly. Two groups of rats were injected daily with gentamicin at respective doses of (80 mg/kg/day) and (150 mg/kg/day) for four consecutive weeks. Control rats were only treated with physiological saline. All treatments were given for four consecutive weeks and all rats were fed on a standard laboratory animal diet pellet and water *ad libitum* and maintained under controlled environmental conditions that included controlled temperature (22 ± 1 °C) and a normal photoperiod (12 h dark and 12 h light).

### 2.1. Blood chemistry

At the end of each week of the experimental period, blood samples were taken from three rats from each group and serum was separated for estimation of the various blood chemical parameters such as free radicals, ALT, AST, ALP, creatinine and urea. A blood chemical analyzer (Reflotron, Roche Co., Germany) was employed for this purpose using the specified analysis kits supplied from analyzer's manufacturer. For measurement of free radicals in blood of the experimental animals, FRAS-4 (Iram-Param Co., Italy) instrument was used and the method d-RAM was applied.

### 2.2. Histological study

Three rats from each group were sacrificed and the kidneys were removed for histological examination. Fresh portions of both kidneys from each rat were cut out rapidly, fixed in neutral buffered formalin (10%) and then dehydrated with grades of ethanol (70%, 80%, 90%, 95% and 100%). Dehydration was then followed by clearing the samples in two changes of xylene. Tissue samples were then impregnated with three changes of molten paraffin wax, then embedded and blocked out. Tissue sections (4 μm) were stained according to Bancroft and Stevens (1999) using the conventional histological stains.

### 2.3. Statistical analysis

All data are presented as values means ± SD. The obtained data were statistically analyzed by SAS (2002) using Duncan test in order to comparison differences between the experimental groups at the level of $P < 0.05$ were considered significant.

## 3. Results

### 3.1. Blood chemistry

Table 1 and Fig. 1 show the results of blood chemistry investigation in all experimental groups. By the end of the first week of experimentation period, all gentamicin-injected animals in G2 (150 mg/kg) died, hence the corresponding blood chemical parameters were not recorded.

### 3.2. Gross examination

In the G1 (80 mg/kg) and G2 (150 mg/kg) groups, the kidneys were moderately swollen and whitish spots on the cortex of kidneys appeared in both of the gentamicin-treated groups by the end of the first week. However, these spots were heterogeneously distributed at the end of the third and fourth weeks of treatment compared with the control group (Figs. 2 and 3).

### 3.3. Histological alterations

Gentamicin-induced marked tubular, glomerular and interstitial alterations in the kidneys of gentamicin-injected rats. The following histological alterations were detected relative to those of the control group.

#### 3.3.1. Tubular alterations

Tubular alterations due to gentamicin treatment appeared early in the form of necrosis, degeneration and vacuolization. Tubular alterations in the kidney appeared by the end of the first week of gentamicin treatment and then increased in severity. These changes included degeneration up to severe necrosis, which included most of the proximal convoluted tubules and to a lesser extent the distal tubules (Fig. 4). The degenerative tubules showed swelling, cytolysis, loss of the proximal tubular brush border and tubular irregularity at 80 mg of gentamicin after the second week of exposure, and became more prominent thereafter.

**Table 1** Blood chemistry parameters estimated at weekly intervals for all experimental groups.

| Parameters | Groups/weeks | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | | | | G1 (80 mg/kg) | | | | G2 (150 mg/kg) | |
| | Week 1 | Week 2 | Week 3 | Week 4 | Week 1 | Week 2 | Week 3 | Week 4 | Week 1 | Weeks 2,3 and 4 |
| ALP (µl/l) M ± SD | 419 ± 00.00$^{B}$ | 413 ± 00.00$^{B}$ | 453 ± 0.00$^{B}$ | 389 ± 00.00$^{D}$ | 320 ± 00.00$^{D*}$ | 199.33 ± 23.10C$^{*}$ | 655 ± 0.00$^{A*}$ | 557 ± 25.98$^{B*}$ | 531.33 ± 31.75$^{A*}$ | |
| ALT (µl/l) M ± SD | 34.6 ± 1.56$^{B}$ | 47 ± 00.00$^{A}$ | 61.4 ± 0.00$^{B}$ | 52.7 ± 4.85$^{BC}$ | 47.03 ± 4.21$^{A*}$ | 46.9 ± 3.98$^{A}$ | 48.20 ± 8.70$^{D*}$ | 47.43 ± 0.93$^{C}$ | 45.47 ± 3.69$^{A*}$ | |
| AST (µl/l) M ± SD | 180.33 ± 21.36$^{CB}$ | 143 ± 0.00$^{C}$ | 182 ± 0.00$^{C}$ | 224 ± 12.12$^{B}$ | 296 ± 34.64$^{A*}$ | 225.67 ± 42.15$^{B*}$ | 200 ± 0.00$^{B*}$ | 246 ± 17.58$^{B}$ | 300.67 ± 47.08$^{A*}$ | |
| Creatinine (mg/dl) M ± SD | 0.5 ± 0.00$^{D}$ | 0.50 ± 0.00$^{B}$ | 0.5 ± 0.00$^{A}$ | 0.50 ± 0.00$^{A}$ | 0.83 ± 0.03$^{D}$ | 1.92 ± 0.00$^{B}$ | 0.50 ± 0.00$^{A}$ | 0.50 ± 0.00$^{A}$ | 3.35 ± 0.37$^{C*}$ | |
| Urea (mg/dl) M ± SD | 37.63 ± 0.75$^{D}$ | 35.10 ± 2.94$^{B}$ | 44.70 ± 8.70$^{C}$ | 49.53 ± 6.12$^{A}$ | 89.73 ± 10.62$^{C*}$ | 37.63 ± 0.75$^{B}$ | 80.20 ± 0.00$^{A*}$ | 55.17 ± 5.61$^{A}$ | 295 ± 8.66$^{A*}$ | |
| Free radicals (U Carr) M ± SD | 365 ± 0.00$^{A}$ | 296 ± 0.00$^{A}$ | 123 ± 0.00$^{B}$ | 322 ± 0.00$^{B}$ | 360 ± 0.00$^{A}$ | 151 ± 6.93$^{C*}$ | 277 ± 0.00$^{A*}$ | 379.67 ± 26.69$^{A*}$ | 351.67 ± 47.08$^{A}$ | |

Different letter within the same row indicates significant differences ($p < 0.05$) between experimental groups for the same blood chemical parameter.

ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase.

Compared with the control animals, the serum level of ALP was the highest at the 3rd week (655 ± 0.00), that of ALT peaked at 3rd week (48.20 ± 8.70) and the highest level of AST serum level was recorded at 1st week (296 ± 34.64).

Regarding creatinine and urea blood levels, the highest level of creatinine was recorded at 2nd week (1.92 ± 0.00) while that of urea was at 1st week (89.73 ± 10.62).

* Significant difference ($p < 0.05$) compared with control group.

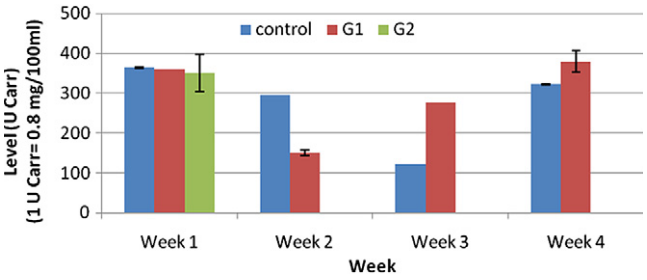


**Figure 1** Level of free radicals in the different experimental groups at weekly intervals. At weeks 3 and 4 the level of free radicals was significantly higher in G1 (80 mg/kg) compared with the control group. The level of free radicals in animals of G1 was increased markedly by elapsing time after gentamicin intoxication. The highest level of free radicals (379.67 ± 26.69 U Carr) was recorded in G1 at the 4th week.

**Figure 2** Morphological appearance of kidney of control rat.

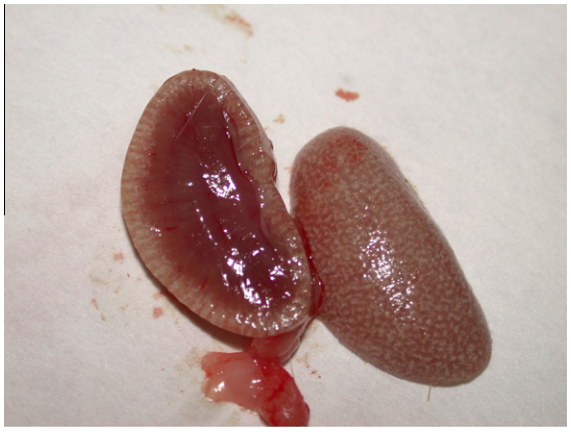

**Figure 3** Morphological appearance of kidney of treated rat showing whitish spots on surface of the kidney and in the outer zone of the cortex.

However, the outer layer of the cortex showed more damage than the medulla, and renal tubules became more affected and showed excessive accumulation of luminal debris (Fig. 5).

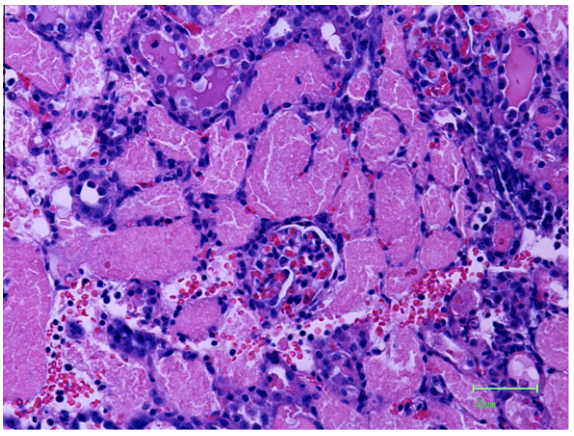

**Figure 4** Photomicrographs showing severe necrosis and scattered hemorrhages (150 mg gentamicin/kg/day) at the end of the first week. H&E 400×.

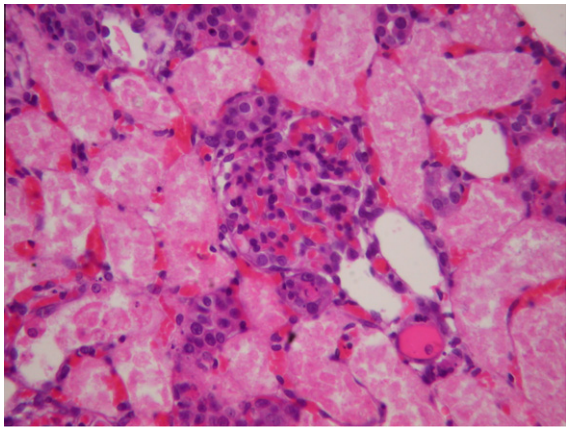

**Figure 5** Photomicrographs showing severe necrosis with cellular debris accumulation in the tubular lumen (80 mg gentamicin/kg/day) at the end of the second week. H&E 400×.

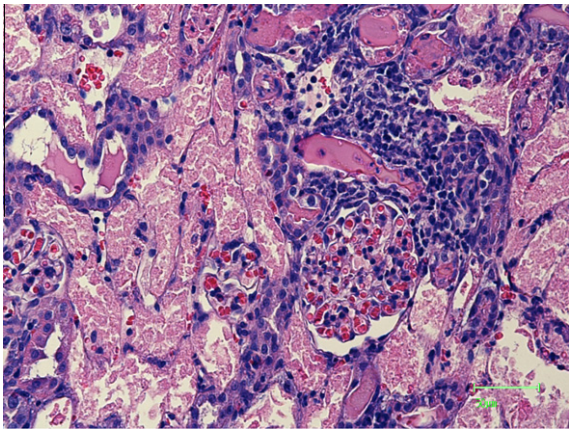

**Figure 6** Photomicrographs showing tubular necrosis and lymphocytes infiltration (80 mg gentamicin/kg/day) at the end of the second week. H&E 400×.

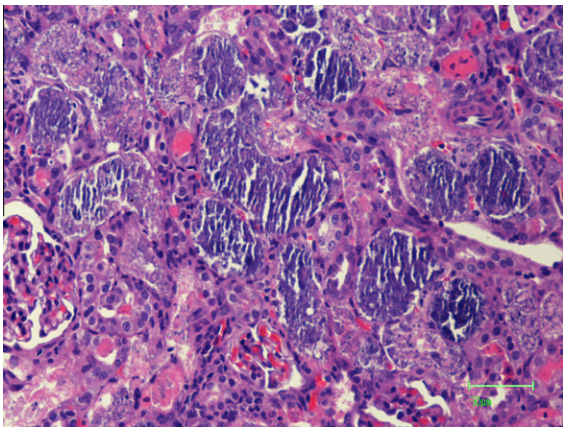

**Figure 7** Photomicrographs showing calcification of the necrotic tubules (80 mg gentamicin/kg/day) at the end of the third week. H&E 400×.

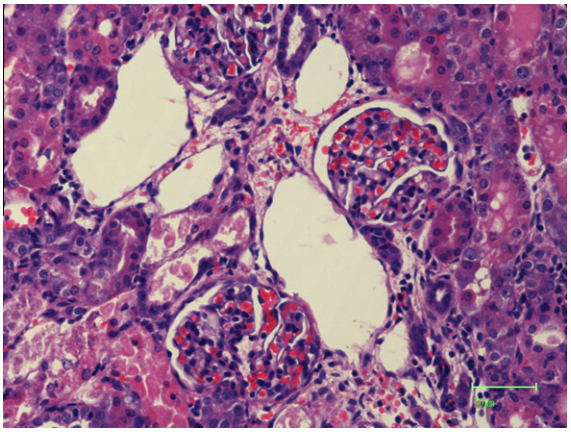

**Figure 8** Photomicrographs showing tubular dilatation with tubular necrosis (80 mg gentamicin/kg/day) at the end of the second week. H&E 400×.

Severe tubular necrosis became more prominent and intertubular lymphocyte infiltration appeared after two weeks of gentamicin treatment at 80 mg (Fig. 6). Calcification of the necrotic renal tubules appeared at the end of the third week of treatment (Fig. 7).

Many tubules exhibited dilation after one week of gentamicin treatment, which then increased in severity (Fig. 8). This alteration appeared first in the inner edge of the cortex and then progressed into the remaining part of the cortex. Some of the dilated collecting tubules in both the cortex and medulla contained dense eosinophilic casts (Figs. 9 and 10).

### *3.3.2. Glomerular alterations*

Alterations in the glomeruli of gentamicin-treated rats appeared from the first week of treatment in the form of mesangial hypercellularity and glomerular endothelial cell proliferation. An increase in the number and volume of mesangial cells appeared in the glomeruli of rats that received 80 mg of gentamicin and more for at least one week. This change increased in severity with an increase in gentamicin dose and period of exposure, and became prominent at the fourth week of treatment (Fig. 11).

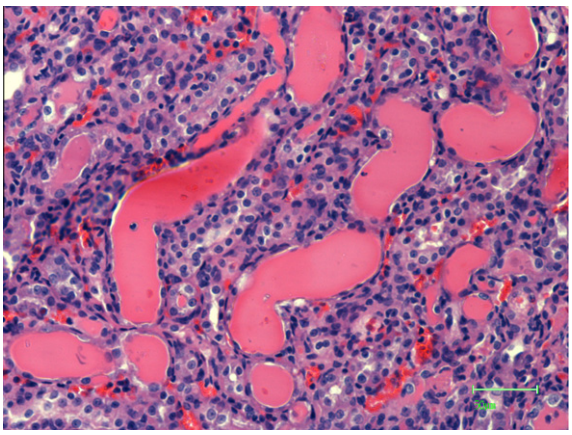

**Figure 9** Photomicrographs showing accumulation of eosinophilic material in the collecting tubules. H&E 400×.

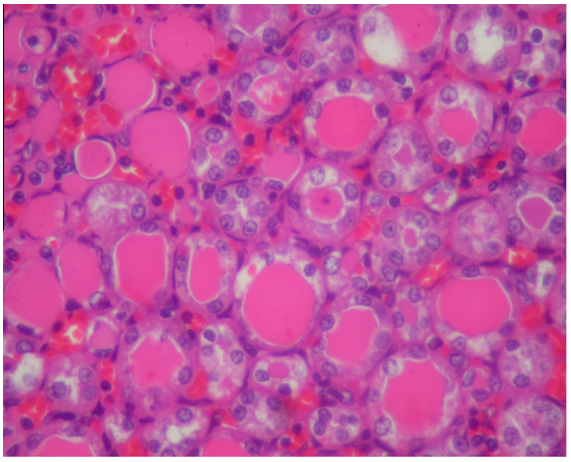

**Figure 10** Photomicrographs showing accumulation of eosinophilic material in the convoluted tubules. H&E 400×.

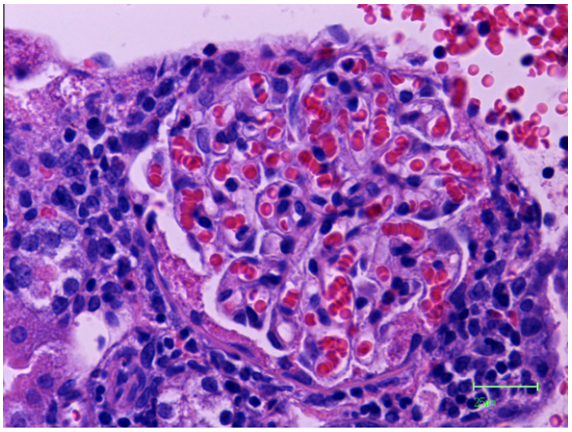

**Figure 11** Photomicrographs showing mesangial glomerular hypercellularity and lymphocytes infiltration (80 mg gentamicin/kg/day) at the end of the second week. H&E 1000×.

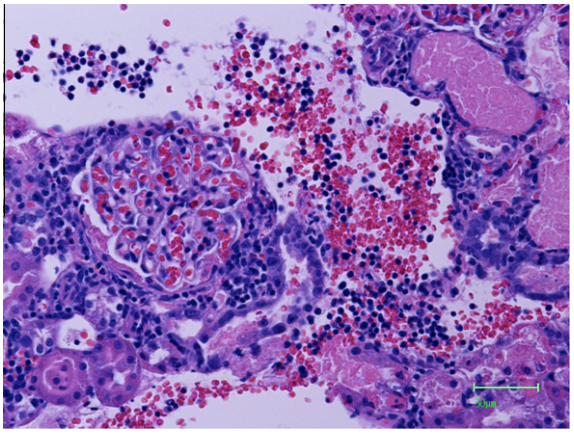

**Figure 12** Photomicrographs showing hemorrhagic foci with tubular necrosis (80 mg gentamicin/kg/day) at the end of the third week. H&E 400×.

### *3.3.3. Interstitial alterations*

The kidneys of gentamicin-treated rats showed cortical interstitial edema with dilatation and congestion of intertubular blood capillaries. The intertubular spaces of gentamicin-treated rats became widely separated from one another due to the accumulation of edematous fluid. Additionally, the kidneys of gentamicin-treated rats showed congestion after the first week of treatment and exhibited intertubular blood capillary dilation. Hemorrhagic foci accompanied tubular necrosis after two weeks of gentamicin treatment (Fig. 12).

The loop of Henle showed very little or no alterations due to gentamicin, the control group showed no significant histological changes during the experimental period.

Rats of the 150-mg group died at the end of the first week of treatment showed severe tubular degenerative and necrotic changes over extensive areas.

## 4. Discussion

Gentamicin is known to generate reactive oxygen species associated with an increase in lipid peroxidation and decrease in antioxidant enzyme activity in the kidney (Banday et al., 2008). Additionally, it acts as an iron chelator by forming an iron–gentamicin complex that is a potent catalyst of radical generation (Khan et al., 2009).

Various blood chemical parameters were estimated for the present experimental animals, these involved the enzymes employed for evaluation of the organ functions. In the present study there was significant ($P < 0.05$) increase in the blood levels of ALT, AST and ALP. The blood levels of ALT, AST and ALP are indicative of the functional efficiency of liver and kidney. The level of these enzymes is very sensitive to any disease conditions of such organs (Tietz, 1996). Blood level of creatinine and urea were also estimated since these two parameters are of special significance to evaluate renal function (Smith et al., 1988; Frank, 1993; Tietz, 1996). The level of free radicals in the blood of the present experimental animals was also assessed to reveal the existence of any oxidative stress (Sener et al., 2002; Ali et al., 2005; Eslami et al., 2011). The observed renal histological changes and the accompanying increased level of ALP indicate the compromised renal function. The study of Kadkhodaee et al. (2005) showed gentamicin-induced renal toxicity and significant increase in the level of ALP. The recorded increased level of ALT indicates functional disorders of the liver, kidney and heart as postulated by Mayne (1994). The presently observed necrobiotic changes of the renal tubules confirm the concept that significant structural changes of the kidney led to significant increase in the blood level of ALT (Smith et al., 1988).

The presently recorded increased blood level of AST also supports the conclusion that gentamicin-induced renal damage is directly related to such increment. Increased blood level of AST is usually coincided with renal damage (Stryer, 1988).

Creatinine is considered as one of the most reliable indicators of the efficiency of renal function (Travlos et al., 1996; Kore et al., 2011; Babu et al., 2011). Increased blood creatinine is strongly related with renal damage (Soliman et al., 2007; Kore et al., 2011). The presently recorded significant increase in blood creatinine was associated with distinct renal structural damage (Chaware et al., 2011; Eslami et al., 2011). As revealed by histological examination, 150-mg group showed renal damage as early as the first week of gentamicin injection while the 80-mg group showed remarkable renal damage by the end of the last week. Abdel-Naim et al. (1999) and Karahan et al. (2005) found that kidney function test had been affected after 5–7 days of gentamicin injection. Both gentamicin-injected groups in the present study showed significant increase of blood urea. Nephrotoxicity, as demonstrated in the present cases, is associated with increased urea in blood (Karahan et al., 2005; El-Ashmawy et al., 2006; Soliman et al., 2007; Zeeni et al., 2007; Chaware et al., 2011; Babu et al., 2011). Presently free radicals were significantly increased in the blood of gentamicin-injected animals. Increased rate of free radicals' production contributes to induction of nephrotoxicity (Sener, 2002; Eslami et al., 2011). Reactive oxygen metabolites, such as superoxide anions and hydroxyl radicals, were supposed to be one of the main contributors of gentamicin-induced nephrotoxicity (Parlakpinar et al., 2003; Ali et al., 2005; Kadkhodaee et al., 2005) through lipid peroxidation (Kumer et al., 2000; Abdel-Raheem et al., 2010). Free radicals released from mitochondria of renal tubular cells were found to be the main factor in induction of gentamicin-induced nephrotoxicity (Kumer et al., 2000; Al-Majed et al., 2002; Abdel-Raheem et al., 2010). Severe and extensive histological alterations in the renal tissue induced by gentamicin as seen in the present work suggest the potential of gentamicin to cause oxidative damage to macromolecules and cellular organelles.

The findings of the present investigation showed that exposure to gentamicin resulted in progressive tubular, glomerular and interstitial histological alterations.

The tubular necrosis and degenerative changes seen in the present work conform with the findings of previous investigations (Can et al., 2000; Kumer et al., 2000; Al-Majed et al., 2002; Ekor et al., 2006; Nitha and Janardhanan, 2008; Kalayarasan et al., 2009; Saleemi et al., 2009; Ali et al., 2011; Dehghani et al., 2011).

The results of the present work showed that the cortex of the kidney was more affected than the medulla as a result of long-term treatment with gentamicin. This might indicate that a relatively higher concentration of gentamicin reaches the cortex via the bloodstream than that entering the medulla. This is in agreement with the findings of Houghton et al. (1976) and

Karahan et al. (2005) which showed that most of the gentamicin accumulates in the renal cortex.

The results of the present work showed that tubular damage was more prominent in proximal convoluted tubules than distal tubules. Other investigators have reported similar findings ( Mingeot-Leclercq and Tulkens, 1999). This could be due to the fact that proximal convoluted tubules are the primary sites of reabsorption and active transport, thus leading to a higher concentration of gentamicin in the epithelial lining of these tubules. This might also suggest that gentamicin toxicity is related to its accumulation in the proximal tubules.

The death of all rats of the 150-mg group after one week of treatment might indicate that a dose of 150 mg/kg body weight for seven consecutive days causes dramatic nephrotoxicity in rats. A previous study showed that a dose of 100 mg/kg body weight for six days resulted in significant nephrotoxicity in rats (Cuzzocrea et al., 2002; Dehghani et al., 2011).

## 5. Conclusion

The findings of this study indicate that exposure to gentamicin is capable of inducing adverse significant blood chemical changes and marked renal histological harmful alterations in *Rattus norvegicus*. The present result may contribute to better understanding of the gentamicin-induced nephrotoxicity in human, and also may be considered as an experimental base of the relevant human studies.

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