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ORIGINAL ARTICLE

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

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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.