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Effect of gentamicin on renal function, oxidative stress, and some markers of antioxidants in male rats

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Abstract
Gentamicin overdose is a frequent cause of nephrotoxicity and possible death, so this study aimed to investigate the effect of gentamicin on serum renal enzyme, oxidative stress, and some markers of antioxidants in male rats.
Methods: A total of 20 rats (3 to 6 months old) raised at high ambient temperature were divided into two equal groups, 10 rats each. The first control group was administered normal saline and the second group of rats was treated with gentamycin (80 mg/kg body weight by intraperitoneal injection) for 30 days. Blood samples were drawn to measure blood urea nitrogen (BUN) levels, serum creatinine, total protein, glutathione (GSH), Malondialdehyde (MDA), and catalase (CAT) levels, and activities were evaluated.
Results: In the gentamicin-treated group, significant increases in blood urea nitrogen activities, serum creatinine, total protein activities, malondialdehyde (MDA) levels, and a significant decrease in catalase (CAT) and glutathione activities were determined compared to the control group.
Conclusion: Administration of gentamycin produces notable biochemical changes in a dose-dependent manner associated with increased renal enzyme, markers of oxidative stress, and decreased antioxidant activity.

Keywords: gentamicin: malondialdehyde: nephrotoxicity: GSH

Introduction

Gentamicin, an aminoglycoside antibiotic, is a broad-spectrum antibacterial drug and has played a special role in the treatment of Gram-negative bacterial infections since the early 20 th century [1]. Although aminoglycosides have benefits, they also have a range of side effects, exemplified by the acute ototoxicity of nephrotoxicity produced by the antibiotic gentamycin [2].

Unfortunately, nephrotoxicity is one of the most adverse effects related to the administration of gentamycin due to tubular damage and thus leads to morphological changes in the apparent histological structure of the kidneys [3]. The canonical mechanism of gentamicin-induced cell damage is not fully understood, but the effect of gentamicin in the generation of free radicals, which is an essential source of pathological events, has been reported [4].

Furthermore, the occurrence of reactive oxygen species is clear evidence of gentamicin-induced nephrotoxic events, in which ROS bind to some large molecules, leading to cell damage and necrosis through multiple mechanisms including protein scavenging, formation of lipid free radicals present in membranes and thus acid degradation nuclear [5].

Material and methods

Twenty healthy male rats weighing about (200 - 300 g) grams, with an average age of 3 to 6 months. It was purchased from the Experimental Animal Center of the College of Veterinary Medicine, Tikrit University and used in the study. This study was performed in accordance with the Guide for the Ethical Care and Use of Laboratory Animals. They were left to acclimatize for one week. They were housed at room temperature in metal cages and kept in stable environmental and nutritional health conditions. Animals were kept on a schedule of diurnal lighting conditions (12 h of darkness and 12 h of light); They were fed on normal food and housed in standard laboratory conditions.

The animals were divided into 10 cages of 5 animals each.

Group I (positive control group) with saline: all rats received 1 mL of normal saline/day orally for 30 days.

Group II (gentamicin-treated group): 10 rats treated with gentamycin (80 mg/kg/day) by intraperitoneal injection for 30 days.

Blood samples (5 ml) were collected through a stab in the eye, and serum samples were prepared for biochemical assays by 10 min centrifugation at 3000 rpm. All serum samples were kept at -80 °C until tests were performed.

Levels of blood urea nitrogen, serum creatinine and total protein were measured supplied by Biomerieux, France.
The levels of, catalase, GSH, and MDA, were measured by spectrophotometer array.

Statistical evaluation
The data were expressed as mean ± SD. Differences between groups were compared by ANOVA using SPSS software (version 16). A p value less than 0.05 was considered statistically significant.

Results
Table (1) shows highly significant increase in the mean values of serum Blood Urea, Creatinine, and Total Protein level in the gentamicin treated groups when compared to the control group (64.91±11.51 vs 29.58±6.81 IU/L: $P < 0.01$), (1.735±0.348 vs 0.696±0.167 IU/L: $P < 0.01$), and (7.01±1.05 vs 6.72±1,003: $P < 0.01$).
Treatment of rat with gentamicin resulted in decrease ($p < 0.05$) in catalase and glutathione activities when compared to the control group (47.185±0.31 vs 53.183±0.15 K/ml: $P < 0.01$), and (0.2912±0.054 vs 0.5115±0.079 mg/mg protein: $P < 0.01$). whereas it markedly increased MDA levels in the serum of treated rats compared to control rats (32.48±2.91 vs 24.47±0.72 mol/L: $P < 0.01$). as shown in Table2.

Table 1: Effect of Gentamicin administration on Blood Urea, Serum Creatinine, and Total Protein of rat.

Parameters	Blood Urea (IU/L)	Serum Creatinine (IU/L)	Total Protein (IU/L)
control	29.58±6.81	0.696±0.167	6.72±1,003
Gentamicin	64.91±11.51	1.735±0.348	7.01±1.05

Table 2: Effect of Gentamicin administration on catalase and glutathione and MDA of the rat.

Parameters	Catalase (K/ml)	Glutathione (mg/mg protein)	MDA (mol/L)
Control	53.183±0.15	0.5115±0.079	24.47±0.72
Gentamicin	47.185±0.31	0.2912±0.054	32.48±2.91

Discussion
The results of the study showed that the levels of urea and creatinine increased significantly in the group treated with gentamicin compared to the control group, a result consistent with several studies.
That gentamicin causes a significant increase in the concentration of some biochemical indicators of kidney function such as blood urea nitrogen (BUN) and creatinine in serum and urine total protein excretion. The explanation for this result is that gentamicin treatment may cause damage to some glomerular cells, as shown in the current study. This leads to a significant increase in urea and creatinine levels [6].
The results of the current study showed a significant increase in the concentration of malondialdehyde, in contrast to the significant decrease in the concentration of reduced glutathione and catalase in the group treated with gentamicin compared to the control group.
Malondialdehyde is currently the most widely used indicator for the detection of oxidative stress and lipid peroxidation products and is often used to reflect the degree of oxidative stress. The body's sweeping antioxidant capacity. Due to the excessive generation of free radicals, the body makes uric acid in an attempt to get rid of the free radicals generated [7]. Under normal physiological conditions, the antioxidant enzymes work to maintain the redox balance of the body and neutralize rampaging free radicals and thus reducing its capacity to damage. They act as radical scavengers, hydrogen donors, electron donors, peroxide decomposer, singlet oxygen quencher, and synergist [8-9]. At the molecular levels, glutathione system is the mother of all antioxidants, the master detoxifier and maestro of the immune system. It plays an important role in cellular defense against oxidantby scavenging ROS as a cofactor of antioxidant enzymes. It is reacts with free radicals such as singlet oxygen, peroxy radicals, and is converted into GSSG and other disulfides. that showed it preventing nature. GSH depletion may cause an impaired cell defense that may lead to tissue [10-11].
The reduction in NADPH and malic NADPH effects on the state of sustainability of the reduced form of the glutathione which is considered an important antioxidant for the cell and its decrease level in the cell leads to the case of oxidation of unsaturated fatty acids and this leads to the oxidative phosphorylation of fats and increase the MDA, that may be a reason for the decreased glutathione [10]. In the present study, there was a significant decrease in GSH activity in the gentamicin-treated group compared to the control reflected the formation formation of free radicals and initiation of lipid peroxidation that may be associated with cellular damage [12].
Catalase is a widely spread antioxidant enzyme in animal tissues. It protects tissues from hyperactive hydroxyl radicals through decomposing hydrogen peroxide [13, 14]. In our study, Cat level was decreased significantly in treated Group due to formation of free radicals in heart and decreases its ability to detoxify reactive oxygen species.

Conclusion
Administration of gentamycin produces notable biochemical changes in a dose-dependent manner associated with increased renal enzyme, markers of oxidative stress, and decreased antioxidant activity

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