Effects of L-Carnitine on kidney histopathology, plasma and tissue total sialic acid, malondialdehyde and glutathione concentrations in response to gentamicin administration in Balb/C mice

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Summary

L-carnitine is an essential cofactor in mitochondrial oxidation of fatty acids with antioxidant and protective effects against lipid peroxidation. We investigated the protective effect of L-carnitine on gentamicin nephrotoxicity and the changes of plasma and kidney total sialic acid concentrations with gentamicin treatments. Twenty four Balb/C mice were divided into 4 groups. Group 1 received subcutaneous (s.c.) isotonic saline daily for 5 days. Group 2 was daily treated with s.c. injection of 500 mg/kg L-Carnitine for 5 days, group 3 was treated with 100 mg/kg of gentamicin (s.c.) injection daily for 5 days, and group 4 with 500 mg/kg L-Carnitine (s.c.) plus 100 mg/kg (s.c.) gentamicin for 5 days. Plasma and tissue glutathione (GSH), malondialdehyde (MDA) and total sialic acid (TSA) concentrations were measured on day 5. Blood urea and creatinine as well as kidney histopathology were also evaluated to assess the nephrotoxic effect of gentamicin. Administration of L-carnitine significantly reduced the gentamicin-induced increases of MDA and TSA concentrations in the plasma and kidneys. In addition, L-carnitine reduced the gentamicin-nephrotoxicity as evidenced by blood urea, creatinine and kidney histopathology. L-carnitine also improved the antioxidant status in the plasma and kidneys of gentamicin treated mice by significantly increasing GSH concentration compared to controls and to mice treated with gentamicin alone. These results suggest that L-carnitine may attenuate gentamicin-induced nephrotoxicity by improving antioxidant status, and reducing tissue lesions in Balb/C mice.

Keywords: Gentamicin - L-carnitine - Nephrotoxicity - Oxidative Stress - Sialic acid.

Introduction

Aminoglycosides including gentamicin are a class of antibiotics which are used in the treatment of serious and life-threatening Gram-negative bacterial infections. However, nephrotoxicity is a major side effect of aminoglycosides which limits their use in the treatment of these infections. Occurrence of renal toxicity caused by aminoglycosides occurs in 5-35 % of cases during the treatment with aminoglycosides [5, 20]. One of the mechanistic explanations regarding gentamicin nephrotoxicity is associated with oxidative stress. Indeed, gentamicin was reported to induce oxi-
dative stress in kidneys, by producing hydrogen peroxide in a dose dependent manner throughout renal cortical mitochondria [37, 38]. Several studies reported that administration of agents with antioxidant properties ameliorated or reduced the nephrotoxic effects of gentamicin [19, 24].

L-Carnitine plays an important role in long chain fatty acid transfer from cytosol to mitochondria for achieving β-oxidation [3, 7, 25, 35]. L-Carnitine is a naturally occurring amino acid-like compound located at the outer surface of the inner membrane. By combination with carnitine to form O-Acylcarnitine, acyl groups could be transferred from cytosolic coenzyme A on the outer surface of mitochondrion membrane, then to the inner surface by exchange with free carnitine using an antiport mechanism. The acyl groups are then transferred from carnitine to coenzyme A within the mitochondrion [17]. Carnitine is also associated with buffering of excess acyl-Co A which is potentially toxic to the cells [7], and it was reported that L-Carnitine had protective effect on lipid peroxidation by reducing formation of hydrogen peroxides and malondialdehyde, and it improved antioxidant status in rats. Moreover, it increased free radical scavenging from the cellular sites [15, 26, 28].

Sialic acids are family of 9-carbon neuraminic acid derivatives which are found in all vertebrates. They are usually found in terminal residues of oligosaccharide chains of mucins, glycoproteins and glycolipids [30, 39]. Sialic acids serve for stabilisation of cellular membranes for cellular interactions, membrane transport, and regulation of glomerular basement membrane permeability. They are also implicated in fixation of various substances onto cell membrane receptors [30]. Serum sialic acid concentrations would have a diagnostic value in various types of diseases (cancers and several types of inflammatory diseases such as arthritis, Crohn’s disease and psoriasis [29, 31]). Increases of the sialic acid concentrations were also correlated with the rate of cardiovascular mortality [18]. In addition, serum sialic acid concentrations are increased in chronic glomerulonephritis, chronic renal failure, chronic liver disease and pneumonia [30].

Gentamicin has been shown to reduce GSH concentrations and glutathione peroxidase activity and increased MDA concentrations leading to oxidative stress and lipid peroxidation in the heart tissue of guinea pig [22]. It has been demonstrated that gentamicin is able to inhibit mitochondrial oxidative phosphorylation in renal mitochondria and to induce formation of free radicals from mitochondrial origin leading to oxidative stress [32, 37]. It is known that protection against free radical-induced oxidative cell injury is carried out by enzymatic and non-enzymatic defence system including GSH [41]. Increase of ROS production and reduction of antioxidant capacities may lead to lipid peroxidation and release of MDA which is used as an indicator of lipid peroxidation, oxidative injury [8], and of cellular membrane damage. Consequently, disorganisation of cell membranes induced by lipid peroxidation would lead to release of sialic acid residues into blood stream. Since L-carnitine has been reported to exhibit antioxidant properties [3, 25], we hypothesized that L-carnitine would partially protect kidneys from gentamicin toxicity. Therefore, we investigated, in this study, the potential protective effects of L-carnitine on renal oxidant status throughout measurement of plasma and renal tissue glutathione (GSH) and malondialdehyde (MDA) concentrations. Moreover, we have confirmed the gentamicin nephrotoxicity by kidney histological examinations and we have followed the plasma and the tissue TSA concentrations in kidneys in order to detect a correlation between aminglycoside nephrotoxicity and variations of this marker.

Materials and methods

ANIMALS AND TREATMENTS

Twenty four Balb/C, 14-16 week old mice (obtained from the University of Kafkas, Animal Research Farm) weighing 25-35 g were randomly divided into 4 groups. Group 1 (control) received subcutaneous (s.c.) injection of isotonic saline solution daily for 5 days. Group 2 (carnitine) was daily treated with subcutaneous injection of 500 mg/kg L-Carnitine (CARNITENE®, Sigma-Tau Industrie Farmaceutiche, Pomezia-Italya) for 5 days, group 3 (gentamicin) with subcutaneous injection of 100 mg/kg gentamicin for 5 days, and group 4 (carnitine + gentamicin) was daily subcutaneously injected with 500 mg/kg L-Carnitine plus 100 mg/kg gentamicin for 5 days. Blood samples were collected from the heart via cardiac puncture under ether anaesthesia in EDTA tubes for plasma GSH, MDA and TSA measurements. All tubes were centrifuged (1 200 g, 4 °C) for 10 minutes to obtain plasma. The plasma samples were kept at -25 °C until they were analyzed. In addition, kidneys were collected for tissue GSH, MDA and TSA concentrations. Briefly, tissues were rinsed with ice-cold 0.9 % NaCl and then 1 g of tissue (four fold) was homogenized in phosphate buffer in 0.1 M KCl (pH 7.4) in an ice bath. The homogenates were centrifuged (1 200 g, 4 °C) for 15 minutes. Total sialic acid (TSA) was measured colorimetrically using a spectrophotometer (UV-1201, Shimadzu, Japan) by the method of SYDOW [34]. For GSH and MDA concentrations, analyses were carried out by the method of BEUTLER [6] and YOSHOIKO [42], respectively. Plasma urea and creatinine concentrations were measured using commercially available kit (Bio-Mérieux, France). In addition, to assess gentamicin nephrotoxicity, kidney histopathology was performed. After fixation in 10 % neutral buffered formalin and embedding in paraffin wax, kidneys were sectioned at 4-6 µm. and stained with haematoxylin-eosin and Periodic acid-Schiff (PAS). Sections of tissues were blindly evaluated by a pathologist, and the pathologic changes were graded according to the severity of lesions.

STATISTICAL ANALYSIS

Differences between the groups were tested by analysis of variance (ANOVA) and Duncan test using SPSS for Windows version 9.0. Data were presented as mean ± standard errors, and p values less than 0.05 were considered significant.
EFFECTS OF L-CARNITINE DURING GENTAMICIN ADMINISTRATION IN BALB/C MICE

Results

The plasma and kidneys TSA, MDA and GSH concentrations according to mice treatments were presented in Table I. Plasma TSA and MDA concentrations were significantly increased in mice treated with gentamicin alone, and significantly lowered in mice received carnitine. In gentamicin plus carnitine treated mice, plasma TSA and MDA concentrations were comparable to those observed in control mice. By contrast, plasma GSH concentrations were the highest in groups received carnitine-treated and gentamicin plus L-carnitine-treated groups compared to the control group. However, the tissue concentration of this marker was significantly lower in mice receiving gentamicin plus L-carnitine than in mice receiving gentamicin alone (Table I). A significant increase of kidney TSA concentration was only evidenced in mice treated with gentamicin alone. The kidney GSH concentration was markedly lowered in the group 3 (treated by gentamicin alone) compared to all the other groups, whereas the maximal value was observed in animals receiving L-carnitine alone (group 2). The tissue GSH concentration in mice co-treated with gentamicin and L-carnitine (group 4) was not statistically different from controls (Table I).

Gentamicin administration induced dramatically increases of blood urea and creatinine concentrations (Table II) showing the alteration of renal function in treated mice. On the other hand, these 2 parameters were unaffected by L-carnitine treatment. Furthermore, the simultaneous administration of carnitine to gentamicin significantly attenuated the impairment of renal function (Table II). Indeed, the increases of plasma urea and creatinine concentrations were significantly reduced in this group compared to gentamicin group.

Histological alterations are presented in Table III. Pathological changes observed in the different groups were limited to the renal cortex. The most prominent lesions consisted of degeneration and necrosis of the proximal tubules. In sections of tissues from mice treated with gentamicin (Fig 1) and gentamicin plus L-carnitine (Fig 2), alterations were characterized by cytoplasmic vacuolation, caryopynosis and cellular enlargements as well as abnormalities ranging from disappearance of nucleus to the necrosis. Degenerative and necrotic changes were more severe in animals treated with gentamicin alone than in those treated with gentamicin plus L-carnitine. Furthermore, widespread regenerative changes were more often observed in the proximal tubules from mice receiving gentamicin plus L-carnitine than from mice treated with only aminoglycoside. The regenerative changes were characterized by the squamous young epithelial cells with hyperchromatic nucleuses and many mitotic figures. The new cells were smaller than normal tubular cells and were localized with closer proximity to the...

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<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TSA (mg/l)</td>
<td>767.9 ± 29.7^b</td>
<td>539.5 ± 30.3^c</td>
<td>919.9 ± 43.9^a</td>
<td>704.3 ± 18.1^b</td>
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<tr>
<td>MDA (µmol/l)</td>
<td>15.95 ± 0.57^b</td>
<td>12.68 ± 0.84^c</td>
<td>20.30 ± 0.78^a</td>
<td>17.68 ± 0.80^b</td>
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<tr>
<td>GSH (mg/l)</td>
<td>81.9 ± 3.0^b</td>
<td>91.4 ± 1.3^a</td>
<td>75.2 ± 1.5^c</td>
<td>92.5 ± 1.7^a</td>
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<td><strong>Kidney Tissue</strong></td>
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<tr>
<td>TSA (mg/g)</td>
<td>2.58 ± 0.10^b</td>
<td>2.96 ± 0.07^b</td>
<td>3.74 ± 0.24^a</td>
<td>2.52 ± 0.18^b</td>
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<tr>
<td>MDA (µmol/g)</td>
<td>0.29 ± 0.06^c</td>
<td>0.27 ± 0.06^c</td>
<td>0.47 ± 0.14^a</td>
<td>0.37 ± 0.07^b</td>
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<td>GSH (mg/g)</td>
<td>0.31 ± 0.01^b</td>
<td>0.44 ± 0.02^a</td>
<td>0.21 ± 0.01^c</td>
<td>0.30 ± 0.01^b</td>
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P < 0.05, results with different superscripts within the same row are significantly different.

Table I. — Plasma and kidney tissue Total sialic acid (TSA), Malondialdehyde (MDA) and Glutathione (GSH) concentrations according to mice treatments: Control Group: Mice injected with isotonic saline/ Carnitine Group: Daily subcutaneous injection of L-carnitine (500 mg/kg) for 5 days/ Gentamicin Group: Daily subcutaneous injection of gentamicin (100 mg/kg) for 5 days/ Gentamicin + Carnitine Group: Daily subcutaneous injection of L-carnitine (500 mg/kg) and gentamicin (100 mg/kg) for 5 days. Results are expressed as means ± standard errors.

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<th>Gentamicin</th>
<th>Gentamicin + Carnitine</th>
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<tr>
<td><strong>Urea (mmol/l)</strong></td>
<td>33.13 ± 1.02^c</td>
<td>34.88 ± 0.84^c</td>
<td>218.73 ± 6.08^a</td>
<td>57.84 ± 1.95^b</td>
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<tr>
<td><strong>Creatinine (mmol/l)</strong></td>
<td>0.36 ± 0.02^c</td>
<td>0.31 ± 0.01^c</td>
<td>2.40 ± 0.05^a</td>
<td>0.80 ± 0.04^b</td>
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P < 0.05, results with different superscripts within the same row are significantly different.

Table II. — Plasma urea and creatinine concentrations according to mice treatments: Control Group: Mice injected with isotonic saline/ Carnitine Group: Daily subcutaneous injection of L-carnitine (500 mg/kg) for 5 days/ Gentamicin Group: Daily subcutaneous injection of gentamicin (100 mg/kg) for 5 days/ Gentamicin + Carnitine Group: Daily subcutaneous injection of L-carnitine (500 mg/kg) and gentamicin (100 mg/kg) for 5 days. Results are expressed as means ± standard errors.
basement membrane forming clusters of young cells. In addition to vascular congestion and extravascular erythrocyte infiltration, focal mononuclear cell clusters were evident in parts of necrotic areas. Cylindrical-shaped necrotic cell remnants were also found within the luminal part of proximal tubules. In PAS-stained sections from all groups, basement membranes of proximal tubules were intact and appeared normal. Necrosis and degeneration were more severe in gentamicin group than in group treated with gentamicin plus L-carnitine (Table III). Furthermore, lesions were rarely observed in control and carnitine groups, and were quite minor (Figures 3 and 4).

### Table III

<table>
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<th>Gentamicin</th>
<th>Gentamicin + Carnitine</th>
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<tbody>
<tr>
<td>Necrosis</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Congestion</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Regeneration</td>
<td>-</td>
<td>-</td>
<td>++</td>
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Pathological alterations were graded and shown as median score for each group with respect to the corresponding parameters. Scoring system: Normal (-), Mild (+), Moderate (++) Severe (+++).

**TABLE III.** — Histological parameters and the degree of pathological alterations according to mice treatments: Control Group: Mice injected with isotonic saline/ Carnitine Group: Daily subcutaneous injection of L-carnitine (500 mg/kg) for 5 days/ Gentamicin Group: Daily subcutaneous injection of gentamicin (100 mg/kg) for 5 days/ Gentamicin + Carnitine Group: Daily subcutaneous injection of L-carnitine (500 mg/kg) and gentamicin (100 mg/kg) for 5 days.
Discussion

In our study, while treatment with gentamicin alone resulted in nephrotoxicity as evidenced by histopathology and increases of blood urea and creatinine concentrations, administration of L-carnitine (500 mg/kg) for 5 days protected Balb/C mice from gentamicin-induced nephrotoxicity. Gentamicin alone induced significant reduction of GSH concentrations and significant increases of MDA and TSA concentrations in plasma and kidneys compared to control mice or to mice treated with carnitine alone or in combination with gentamicin.

Oxidative stress is one of the leading factors in the initiation of renal disease processes such as acute or progressive renal failure, tubulointerstitial nephritis, glomerulonephritis, obstructive nephropathy and tubular hypertrophy [13]. Increased oxidative stress could be due to the exogenous action of toxic chemicals and drug side effects [8]. Agents that alter mitochondrial respiration have been reported to induce generation of free radicals [37, 38]. Because gentamicin can inhibit mitochondrial oxidative phosphorylation in renal mitochondria [32], nephrotoxicity could be caused by generation of free radicals and oxidative stress [37].

The increase of plasma TSA concentrations in gentamicin treated mice would be related to massive release of membrane structures containing sialic acids into blood flow and would evidence the cellular deleterious effects of aminoglycosides. Indeed, by inhibiting phospholipases, gentamicin induced accumulation of phospholipids within lysosomes [20, 27], and the rupture of these organelles lead to release of membrane elements including lipid bound sialic acids. Furthermore, the induction of oxidative stress and the consequent membrane lipid peroxidation would contribute to release of sialic acids from cellular membranes.

Glutathione belongs to antioxidant defence systems and prevents harmful effects of free radicals by scavenging hydroxyl radicals and singlet oxygen [10, 41]. Therefore, reduced GSH may contribute to decrease antioxidant potential leading to oxidative stress and consequently to nephrotoxicity.

The oxidative stress is characterized by enhancement of free radical formation leading to lipid peroxidation and breakdown of cellular membranes. By oxidizing polyunsaturated fatty acids of membrane phospholipids, reactive oxygen species induce chain radical reactions, whose end products, especially malondialdehyde (MDA), can be used as markers of oxidative damage [8, 11]. Consequently, our results confirm that gentamicin has induced an oxidative stress in kidney, evidencing by increase of plasma and kidney MDA concentrations, and that L-carnitine exhibited some suppressive effects on spontaneous oxidative stress or induced by aminoglycosides. Various agents with antioxidant properties have been successfully used to ameliorate gentamicin-induced nephrotoxicity [1, 19, 36, 40]. ALI and BASHIR [1] reported that administration of superoxide dismutase in rats ameliorated signs of gentamicin nephrotoxicity, and prevented depletion of GSH in kidney tissue. Furthermore, gentamicin treatment in rats increased lipid peroxidation and resulted in decreases of GSH concentration as well as tissue hypoxia in kidneys. However, N-acetylcysteine, which is known to have antioxidant properties, reversed these effects [12]. Similarly, gentamicin administration in rats resulted in increase blood urea and creatinine concentrations, tubular cell necrosis and renal oxidative stress shown by an increase of nitrotyrosine. These effects were ameliorated by an antioxidant, dialyl sulfide [24].

The results of the present study also demonstrated that gentamicin caused nephrotoxicity in the proximal tubules of mice kidney as evidenced by histological changes, increases of tissue MDA as well as decreases of tissue GSH. While kidney histological alterations were typical of acute gentamicin nephrotoxicity in gentamicin treated group, lesions in the group receiving simultaneously gentamicin and L-carnitine were mild and regenerative changes were much more prominent. Although mechanisms of the nephrotoxic effects of aminoglycosides are still unclear, several hypotheses have been postulated. Among these, the localisation of gentamicin into the lysosomes of tubular cells and the subsequent lipase inhibition by the drug would lead to the accumulation of phospholipids in cells, then to lysosome disruption and finally to cell necrosis [27, 33]. It was further suggested that increased amounts of phosphatidylinositol and phosphatidylcholine associated with decreased sphingomyelin contents could alter events involved in the degradation of phospholipids [33]. Gentamicin accumulation occurs mostly in lysosomes as well as in the Golgi apparatus and mitochondria possibly via retrograde trafficking. In mitochondria, gentamicin could affect mitochondrial functions by inhibiting renal mitochondrial phosphorylation [32]. MOUEDDEN et al. [21] demonstrated that gentamicin is able to induce apoptosis which was directly correlated with phospholipidosis and cell proliferation. Coupled to the inhibition of growth factors due to phosphatidylinositol phospholipase C and protein kinase C inhibition, mitochondrial dysfunction ultimately caused ATP depletion, release of Apafs (Apoptosis activating factors, particularly cytochrom c) and activation of caspases directly responsible for the apoptosis characteristic cytological changes.

The potential protective effects of some chemicals exhibiting antioxidant properties on gentamicin nephrotoxicity were examined. For example, some agents such S-allylcysteine [19], diallysulfide [24], and N-acetylcysteine [12] have been demonstrated to prevent functional toxicity and also to ameliorate histological damage in the kidneys in response to gentamicin treatment. In addition, L-carnitine has been shown to prevent doxorubicin-induced apoptosis in rat cardiac myocytes [2]. The doxorubicin cardiac toxicity was mediated by increase of free radical production and by ceramide accumulation. By limiting ceramide generation, L-carnitine protected cardiomyocytes from doxorubicin toxicity [2]. Moreover, numerous studies have previously demonstrated the protective effects of L-carnitine on the toxicity of various drugs involving free radicals. L-carnitine reduced methamphetamine neurotoxicity, mediated by peroxynitrites [4], brain injury in neonates related to hypoxia and ischemia and during ischemia-reperfusion cases [23] and chronic renal failure with oxidative stress in Wistar rats [38]. Acetyl-L-carnitine (an esterified form) reduced the lipid peroxidation and oxidative stress in aged rats [14, 16].

Several mechanisms could explain the protective effects of L-carnitine against gentamicin nephrotoxicity. By increasing oxygen utilization and enhancing ATP formation throughout
fatty acid β-oxidation, L-carnitine could prevent gentamicin induced mitochondrial oxidative damage. Secondly, L-carnitine could offer protection by directly increasing tissue antioxidant capacities since L-carnitine has been shown to increase GSH concentrations [9] (This effect has been also observed by an increase of plasma and tissue GSH concentrations in our study). Therefore, it may provide a buffer capacity for free radicals generated and may protect against lipid peroxidation.

In conclusion, we suggest that L-carnitine is able to ameliorate gentamicin induced adverse effects by improving antioxidant status and reducing lipid peroxidation as well as protecting cellular membranes. However, the exact mechanisms of these effects warrant further investigations.

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