Protective effect of Melatonin, Rosuvastatin and their combination against Amikacin induced nephrotoxicity in rats.

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ABSTRACT
The current work was conducted to study the possible protective effect of melatonin, rosuvastatin and combination of them on nephrotoxicity induced by amikacin in rats. Forty adult male albino rats were allocated into five groups (8 animals each) and were treated daily for 2 weeks as follows:

Group I: (Control group) treated with dimethylsulfoxide (DMSO) orally.
Group II: injected with daily dose of (120 mg/kg/IP) of amikacin.
Group III: injected with daily dose of amikacin (120 mg/kg) with daily oral dose of melatonin (10 mg/kg).
Group IV: injected with daily dose of amikacin (120 mg/kg) with daily oral dose of rosuvastatin (10 mg/kg).
Group V: animals were injected with daily dose of amikacin (120 mg/kg) simultaneously treated with a combination of melatonin and rosuvastatin with the previously mentioned doses respectively. After 2 weeks blood samples were obtained for biochemical analyses. Then, rats were sacrificed and the kidney were collected for tissue homogenization and histopathological study. Results: amikacin administration induced significant increase in kidney weight, serum urea and creatinine, tumor necrosis factor (TNF-α), tissue malondialdehyde (MDA) levels and reduction in superoxide dismutase (SOD) activity. Simultaneous administration of melatonin and rosuvastatin treatment with amikacin significantly lowered the elevated serum urea and creatinine concentration, kidney weight, serum TNF-α and renal MDA and significantly enhance renal SOD activity with improvement of the kidney histological findings in comparison with group II. Conclusion: it could be concluded that combination of melatonin and rosuvastatin may be useful for reducing the nephrotoxic effects of amikacin.

Keywords: Melatonin, Rosuvastatin, Amikacin, BUN, Creatinine, TNF-α, MDA, SOD, Renalhistopathology


Introduction
Aminoglycosides are potent bactericidal antibiotics; they are act particularly against aerobic, gram-negative microorganisms (1). Amikacin is one of the most important aminoglycoside antibiotics, mostly used for treatment of severe, hospital-acquired infections with multidrug resistant Gram negative bacteria such as Acinetobacter, Enterobacter and Pseudomonas aeruginosa. (2) Amikacin has high anti-bacterial efficacy, rapid onset of action, synergy with other ß-lactam antibiotics, low resistance and low cost despite all their beneficial effects, their clinical uses is restricted because of nephrotoxicity and ototoxicity (3).

Aminoglycosides nephrotoxicity have been documented in numerous experimental studies (4-5). One mechanism of this toxicity is believed to be involved the generation of reactive oxygen radical species that are play a key role in a pathogenesis of aminoglycosides nephrotoxicity and it also has been shown that toxicity might be prevented with several antioxidants (6-7). Additionally, it has been demonstrated that aminoglycosides form a complex with mitochondrial Fe⁺³ to catalyze the formation of free radicals (8).

Melatonin (N-acetyl-5-methoxytrypamine) is a secretory product of pineal gland, might have a protective effect against free oxygen radicals by acting as a direct radical scavenger and indirect by up regulating the expression of several intracellular antioxidative enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and glutathione reductase (GRd) as well as melatonin stimulates the synthesis of important endogenous antioxidant such as glutathione GSH (9).

It has been shown that melatonin attenuate the nephrotoxicity induced by a wide range of drugs that may cause oxidative stress in the cells of kidney including vancomycin, amikacin, and cisplatin (10-12). Rosuvastatin belong to statins group of cholesterol-lowering agents that effectively decrease serum cholesterol levels by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, thus reducing the production of mevalonate and cholesterol biosynthesis, therefore it is effective in prevention the primary and secondary cardiovascular diseases. Rosuvastatin has anti-inflammatory, immunomodulatory, antioxidant activities (13-15).

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Materials and methods

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Drugs and chemicals

Amikacin (Zentiva, Turkey), Melatonin (NATROL, USA) and Rosuvastatin (Astra Zeneca, UK) were purchased from commercial sources.

Test animals

The experimental protocols used in this study were approved by the ethical Committee of the College of Medicine/Al Nahrain University and were performed in accordance with Iraqi center for cancer and medical genetics researches for the Care and Use of Laboratory Animals. Male Wistar albino rats with an initial body weight of (250-450) g were used in this study. The animals were kept in groups and housed in stainless steel cages under standard environmental conditions at a temperature of 24 ± 3°C, with 12 h light/dark cycles. Standard commercial diet and water were available ad libitum.

Experimental design

Forty male Wistar albino rats were randomly divided in to five groups each containing eight rats:

Group I: served as control group and treated with 0.5 ml/kg (body weight) of 1% dimethylsulfoxide (DMSO) orally once daily and continued till day 14.

Group II: was injected with amikacin (120 mg/kg/day, i.p.) for 14 consecutive days (23).

Groups III and IV: were administered with melatonin (10 mg/kg/day, p.o.)(24) and rosuvastatin (10 mg/kg/day, p.o.)(18) (Through a gavage), both are dissolved in DMSO and administrated orally one hour before injections of amikacin (120 mg/kg/day, i.p.) for 14 days respectively.

Group V: was administered a combination of melatonin (10 mg/kg/day, p.o.) and rosuvastatin (10 mg/kg/day, p.o.) both are dissolved in DMSO and administrated orally one hour before injections of amikacin (120 mg/kg/day, i.p.) for 14 days and then all animals were sacrificed at day 15.

Preparation of blood samples and tissue

After 14 days of treatment, the weight of animals was measured after they were anesthetized by inhaled chloroform. Blood samples (4-6 ml) were taken by cardiac puncture, and then the samples were left to clot, and then centrifuged at 3000 rpm for 15 minutes to separate serum, which was stored at -20°C until used for the determination of creatinine, urea, superoxide dismutase and tumor necrosis factor (TNF-α) (25) after which animals were sacrificed by cervical dislocation, kidneys quickly being removed, washed with ice/cooled physiological saline and absolute and relative kidney to body weight ratio were measured for all rats. Left kidneys were placed in chilled phosphate buffer solution (PH 7.4) at 4°C, blotted with filter paper and weighed then one gram of it was taken to prepare 10% tissue homogenate using the same buffer solution utilizing tissue homogenizer for 1 minute at 4°C. While the right kidneys were kept in formaldehyde (10%) and utilized for histological examination using paraffin section technique (26).

Kidney and body weight measurement:

Body weights were measured for all groups at 0th and 15 day and the kidney weights were measured immediately after animals were sacrificed to calculate relative (kidney to body weight ratio) for all rats.

Determination of serum creatinine level

Serum creatinine concentrations were determined according to Jaffe reaction using ready-made kit for this purpose. This was expressed in (mg/dl) (27).

Determination of serum urea level

Serum urea levels were determined using urease-modified Barthelot reaction by a ready-made kit for this purpose. This was expressed in (mg/dl) (28).

Determination of serum superoxide dismutase (SOD)

The serum concentration of SOD levels were determined by using ELISA technique, principle of the assay employs the competitive inhibition enzyme immunoassay technique using a commercially available SOD assay kit (Elabscience) according to the manufacturer's instructions. This was expressed in (ng/ml)

Determination of serum tumor necrosis alpha (TNF-α)

The serum concentrations of TNF-α were determined by using Sandwich ELISA technique, using a commercially available TNF-α assay kit (Elabscience) according to the manufacturer's instructions. This was expressed in (pg/ml) (29).

Measurement of tissue malondialdehyde (MDA)

The concentration of renal tissue MDA level was measured by using ELISA technique, principle of the assay employs the competitive inhibition enzyme immunoassay technique. This was expressed in (ng/ml)(30).

Histopathological study

Right kidney of each animal was removed and fixed in 10% of neutral formalin and processed. Paraffin sections 5µm thick were stained with hematoxylin and eosin. The histopathological changes were evaluated in several sections from each group.

Statistical analysis

The results were expressed as mean ± SEM. Analysis of the results was performed using Paired-Sample-t test by SPSS 23.0 that was used for the evaluation of statistical significance. Difference was considered significant at P < 0.05 level.
Results

Effect of different treatment on kidney and body weight

Relative kidney weight highly significant increased ($P<0.001$) in the amikacin treated group compared with control group which could be ameliorated significantly by melatonin and a combination of melatonin androsuvastatin treatment ($P<0.001$). Whereas rosuvastatin treatment didn’t show any effect on relative kidney weight in comparison with amikacin treated group ($p>0.05$). Body weight was not affected in any animal groups as seen in table 1.

Table 1. Effects of melatonin and rosuvastatin and their combination on amikacin/induced alterations in the body weight and kidney weights

<table>
<thead>
<tr>
<th>Group</th>
<th>Kidney weight (g) (Mean ±SEM)</th>
<th>Body weight (g) (Mean ±SEM)</th>
<th>Per body weight (%) (Mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>1.031 ± 0.04</td>
<td>312.37 ± 14.08</td>
<td>0.331 ± 0.007</td>
</tr>
<tr>
<td>Amikacin group</td>
<td>1.295 ± 0.02 a</td>
<td>300.62 ± 7.62 aNS</td>
<td>0.431 ± 0.004 a**</td>
</tr>
<tr>
<td>Melatonin group</td>
<td>1.120 ± 0.07aNS, bNS</td>
<td>331.25 ± 27.84 aNS, b</td>
<td>0.343 ± 0.012 aNS, b**</td>
</tr>
<tr>
<td>Rosuvastatin group</td>
<td>1.047 ± 0.03 aNS, b</td>
<td>251.37 ± 17.25 aNS, b</td>
<td>0.424 ± 0.016 a, bNS</td>
</tr>
<tr>
<td>A combination</td>
<td>1.108 ± 0.05aNS, b</td>
<td>326.00 ± 20.23 aNS, bNS</td>
<td>0.343 ± 0.015 aNS, b**</td>
</tr>
</tbody>
</table>

N=Number of animals; SEM = standard error of mean, a=Comparison with control group; b=Comparison with amikacin group, NS= Not statistically significant ($p>0.05$); *= statistically significant ($p<0.05$); **= highly statistically significant ($p<0.001$)

Effect of different treatments on serum creatinine levels

The mean of serum creatinine level of the control group (±SEM) was (0.617 ± 0.03) (mg/dl). It was significant elevated in amikacin group ($P<0.05$) in which the mean of serum creatinine level reached (1.261 ± 0.10) (mg/dl). In the melatonin and rosuvastatin groups, the means were (0.720 ± 0.07 and 0.800 ± 0.04) (mg/dl) respectively, which are significantly reduced in comparison with amikacin group ($P<0.05$), while the mean of serum creatinine level in a combination of melatonin and rosuvastatin groups was (0.636 ± 0.04) which are highly significantly reduced in comparison with amikacin group ($P<0.001$) as shown in the table 2.

Effect of different treatments on serum urea levels

The mean of serum urea level of the control group (±SEM) was (42.06 ± 1.73) (mg/dl). It was highly significantly elevated in amikacin group ($P<0.001$) in which the mean of serum urea level reached (94.62 ± 3.34) (mg/dl). In the groups treated with melatonin and a combination of melatonin and rosuvastatin, the means were (58.65 ± 7.45 and 55.62 ± 3.79) (mg/dl) respectively, which are highly significantly reduced in comparison with amikacin group ($P<0.001$) while the mean of serum urea level in groups treated with rosuvastatin was (71.85 ± 5.54 which are significantly reduced in comparison with amikacin group ($P<0.05$) as shown in the table 2.

Table 2. Effects of melatonin and rosuvastatin and combination of them on Amikacin/induced alterations in the serum urea and creatinine.

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum Creatinine (Mean ± SEM) (mg/dl)</th>
<th>Serum urea (Mean ± SEM) (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>0.617 ± 0.03</td>
<td>42.06 ± 1.73</td>
</tr>
<tr>
<td>Amikacin group</td>
<td>1.261 ± 0.10 a*</td>
<td>94.62 ± 3.34 a**</td>
</tr>
<tr>
<td>Melatonin group</td>
<td>0.720 ± 0.09a NS, b*</td>
<td>58.65 ± 7.45 a NS, b**</td>
</tr>
<tr>
<td>Rosuvastatin group</td>
<td>0.800 ± 0.04a <em>, b</em></td>
<td>71.85 ± 5.54 a <em>, b</em></td>
</tr>
<tr>
<td>(rosuvastatin+melatonin) group</td>
<td>0.636 ± 0.04 a NS, b**</td>
<td>55.62 ± 3.79 a NS, b**</td>
</tr>
</tbody>
</table>

N=Number of animals; SEM = standard error of mean, a=Comparison with control group; b=Comparison with amikacin group, NS= Not statistically significant ($p>0.05$); *= statistically significant ($p<0.05$); **= highly statistically significant ($p<0.001$)

Effect of different treatments on serum TNF-α levels

The mean of serum TNF-α level of the control group (±SEM) was (62.87 ± 1.85) (pg/ml). It was highly significantly elevated in amikacin group ($P<0.001$) in which the mean of serum TNF-α level reached (90.00 ± 1.80) (pg/ml). In the groups treated with melatonin and a combination of melatonin and rosuvastatin, the means were (69.00 ± 2.81 and 64.50 ± 2.67) (pg/ml) respectively, which are highly significant reduced in comparison with amikacin group ($p<0.001$) while the mean of serum TNF-α level in group treated with rosuvastatin was (73.50 ± 2.23)(pg/ml) which are significantly reduced in comparison with amikacin group ($p<0.05$) as shown in the table 3.
Effect of different treatments on serum SOD levels

The mean of serum SOD level of the control group (±SEM) was (25.26 ± 0.58) (ng/ml). It was highly significant reduced in amikacin group (P<0.001) in which the mean of serum SOD level reached (12.87±0.46) (ng/ml). In the groups treated with melatonin, rosuvastatin and a combination of melatonin and rosuvastatin, the means of serum SOD level were (23.33±0.95, 21.25±0.59 and 25.10±0.54) (ng/ml) respectively, which are highly significantly elevated in these groups in comparison with amikacin group (P<0.001) as shown in the table 3.

Effect of different treatments on renal tissue levels of MDA

The mean of renal tissue level of MDA in the control group (±SEM) was (41.62 ± 2.35) (ng/ml). It was significant elevated in amikacin group (P<0.05) in which the mean of renal tissue level of MDA reached (89.12 ± 9.89) (ng/ml). In the groups treated with melatonin, rosuvastatin and a combination of melatonin and rosuvastatin, the means of renal MDA level were (45.87 ± 1.93, 52.12 ± 7.70 and 41.37 ± 3.42) (mg/ml) respectively, which are significantly reduced in comparison with amikacin group (P<0.05) as shown in the table 3.

Table 3 Effects of melatonin and rosuvastatin and combination of them on Amikacin/induced alterations in the tissue MDA, serum TNF-α and serum SOD levels.

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum TNF-α (mean ± SEM) (pg/ml)</th>
<th>Serum SOD (mean ± SEM) (ng/ml)</th>
<th>Renal tissue MDA (mean ± SEM) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>62.87 ± 1.85</td>
<td>25.26 ± 0.58</td>
<td>41.62 ± 2.35</td>
</tr>
<tr>
<td>Amikacin group</td>
<td>90.00 ± 1.80 a**</td>
<td>12.87 ± 0.46 a**</td>
<td>89.12 ± 9.89 a**</td>
</tr>
<tr>
<td>melatonin group</td>
<td>69.00 ± 2.81 a**,b**</td>
<td>23.33 ± 0.95 a**,b**</td>
<td>45.87 ± 1.93 a**,b**</td>
</tr>
<tr>
<td>rosuvastatin group</td>
<td>73.50 ± 2.23 a,b*</td>
<td>21.25 ± 0.59 a*,b**</td>
<td>52.12 ± 7.70 a*, b*</td>
</tr>
<tr>
<td>(rosuvastatin+melatonin) group</td>
<td>64.50 ± 2.67 a**,b**</td>
<td>25.10 ± 0.54 a**,b**</td>
<td>41.37 ± 3.42 a**,b**</td>
</tr>
</tbody>
</table>

N=Number of animals; SEM = standard error of mean, a=Comparison with control group; b=Comparison with amikacin group, NS= Not statistically significant (p>0.05); *= statistically significant (p˂0.05); **= highly statistically significant (p˂0.001)

Effect of treatments on histopathological score

The effect of amikacin on the renal functions showed significant elevation (p<0.05) in the histopathological scores of renal tissue of rats treated with amikacin (3.75 ± 0.16) compared to the corresponding value in the control group (0.00 ± 0.00) of animals. In the groups treated with melatonin, rosuvastatin and a combination of melatonin and rosuvastatin the value of histopathological scores of renal tissue of rats were (2.12 ± 0.12, 2.87 ± 0.12 and 0.875 ± 0.12) respectively, which are significantly reduced in comparison with amikacin group (P<0.05) as shown in the table 4. Histopathological examination of renal sections in different groups showed in figures 1, 2, 3, 4 and 5.

Table 4 Histopathological scores of study groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Histopathological scores (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td>Amikacin group</td>
<td>3.75 ± 0.16 a*</td>
</tr>
<tr>
<td>melatonin group</td>
<td>2.12 ± 0.12 a,b*</td>
</tr>
<tr>
<td>rosuvastatin group</td>
<td>2.87 ± 0.12 a,b*</td>
</tr>
<tr>
<td>(rosuvastatin+melatonin) group</td>
<td>0.875 ± 0.12 a,b*</td>
</tr>
</tbody>
</table>

N=Number of animals; SEM = standard error of mean, a=Comparison with control group; b=Comparison with amikacin group, NS= Not statistically significant (p>0.05); *= statistically significant (p<0.05); **= highly statistically significant (p< 0.001)
Figure 1: Section of the kidney of control group show normal structure appearance of the glomerulus and renal tubule. (G) Glomerulus, (PCT) Proximal tubule, (B) Bowman capsule. Magnification : (40X); Staining: H&E.

Figure 2: Section of the kidney of amikacin treated group showing renal tubular swelling (blue arrow), vacuolation (green arrow), desquamation (black arrow) and necrosis (yellow arrow). (G) Glomerulus, (PCT) Proximal tubule, (B) Bowman capsule. Magnification : (40X); Staining: H&E.
Figure 3: Section of the kidney of melatonin treated group showing renal tubular swelling (blue arrow), vacuolation (green arrow) and cellular desquamation (black arrow) with absence of necrosis. (G) Glomerulus, (PCT) Proximal tubule, (B) Bowman capsule. Magnification: 40X; Staining: H&E.

Figure 4: Section of the kidney of rosuvastatin treated group showing renal tubular swelling (blue arrow), vacuolation (green arrow), desquamation (black arrow), and necrosis (yellow arrow). (G) Glomerulus, (PCT) Proximal tubule, (B) Bowman capsule. Magnification: 40X; Staining: H&E.
Discussion

Nephrotoxicity is a major clinical complication of aminoglycoside antibiotics. Amikacin is one of the most important aminoglycosides which is widely used for treatment of severe gram-negative bacterial infections. In spite of its clinical usefulness, there are constraints in using this drug as it is cause nephrotoxicity and ototoxicity.(31) It was early believed that aminoglycosides nephrotoxicity result from its re-absorption and accumulation in the renal proximal tubular cells (32). Additionally, it has been reported that the free radicals are responsible for tubuloglomerular degeneration of the kidney, which is the pathogenesis of the oxidative stress associated with aminoglycosides nephrotoxicity (33). The results of our study demonstrate that the amikacin had induced nephrotoxicity by causing significant elevation in the kidney/body weight ratio comparing with the control group (tables1) and this is may be attributed to the fact of the injection of nephrotoxic drugs lead to increase in the kidney weight and this was caused by swelling of renal tissue and this results are compatible with a studies done by (34-35).

In the present study, amikacin had induced nephrotoxicity by significant elevation of serum creatinine and urea levels in comparison with the control group (tables2). The elevation in serum creatinine and urea levels may be attributed to generation of reactive oxygen species (ROS) that play central key role in the mechanisms that lead to decrease glomerular filtration rate and renal tubular necrosis, so this will lead to reduced creatinine and urea clearance that is associated with elevation of serum urea and creatinine and this results are agreement with studies done by (36-38).

In the present study, amikacin had induced nephrotoxicity by causing significant elevation of serum TNF-α level in comparison with the control group (table3) and this is may be attributed to the formation of ROS which activates nuclear factor kappa B (NF-KB) that has a key role in the initiating of inflammatory events and inducing renal damage (36,38)

In the present study, amikacin had induced nephrotoxicity by causing significant reduction of serum SOD level in comparison with the control group (table3) and this is may be related to the ability of aminoglycosides to generate ROS and these radicals are inactivate the antioxidant enzymes and alter their levels within renal tissues. When ROS production exceeds normal level of antioxidant enzymes, these enzymes are insufficient to metabolize all these radicals. Our results are in agreement with study done by (37).

Amikacin had induced nephrotoxicity by causing highly significant elevation of tissue MDA level comparing with the control group (table 3) and this is may be attributed to the involvement of oxidative stress in the nephrotoxicity and free radical production through lipid peroxidation these results are compatible with other studies (38-41). In the current work amikacin nephrotoxicity caused severe histopathological changes with high scores, these changes involvetubular cell swelling, vacuolation, desquamation, vascular congestion and necrosis these changes involving about 75% of renal tubules in comparison with control group (table 4). It was reported that amikacin induce renal tissue damage via excessive oxidative stress and inflammation (38, 42-43).

Effect of melatonin against amikacin induced nephrotoxicity

The results of our study showed that treatment with melatonin induced significant decrease in kidney weight, serum levels of creatinine, urea, TNF-α, tissue MDA and histopathological scores as well as elevation in serum levels of SOD as compared to amikacin group (tables 1, 2, 3and 4) Melatonin prevents nephrotoxicity directly by scavenging ROS and RNS including hydroxyl radical (·OH), singlet oxygen (O2·1), hydrogen peroxide (H2O2), superoxide radical (O2·−), nitric oxide (NO) and peroxynitrite anion (ONOÓ) and reduce their generation by inhibiting the activity of nitric oxide synthase (iNOS) (44). So melatonin exert its antioxidant effect either directly by scavenging free radicals or indirectly by increasing the activity of antioxidant enzymes; superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (Grd) and the expression of endogenous antioxidant defense (glutathione). These antioxidant enzymes has an important role in metabolism of free radicals to less reactive species and then decreases of highly toxic by-products i.e., when SOD dismutates O2·− to H2O2 which in turn, decrease free radical mediated cellular damage ; CAT converts H2O2 to oxygen and water , GPX oxidizes GSH to glutathione disulfide (GSSG) then Grd reduce GSSG to GSH (45-46) therefore, the antioxidant capability of melatonin involve reducing the ROS production which is in turn leading to attenuation renal tubular necrosis,
Effects of rosuvastatin against amikacin induced nephrotoxicity

In the present study, rosuvastatin treatment results in an improvement of serum levels of creatinine, urea, TNF-α, SOD and tissue MDA as compared to amikacin group (Tables 2, 3) as well as, rosuvastatin reduces scores of the histopathological changes as compared with amikacin group (Table 4) whereas rosuvastatin treatment didn’t show any effect on relative kidney weight in comparison with amikacin treated group (Tables 1). Rosuvastatin reduce serum level of urea and creatinine by improving endothelial function, increase the bioavailability NO synthetase lead to improve the GFR or may be secondary to decreased ROS formation (54-55). Rosuvastatin lower serum TNF-α level and this is probably due to a reduction in the activity of nuclear factor kappa B (NF-Kb) and elevation in protein kinases B (PKB) activity (56-57).

Rosuvastatin enhance serum SOD level and this is may be attributed to its ability for inhibition of NADPH oxidase, which occur in the formation of superoxide anion so by inhibiting this enzymes, rosuvastatin may reduce the amount of superoxide radical, therefore SOD may be insufficiently consumed, and consequently, lead to an elevation in its level (58).

Rosuvastatin lowers tissue MDA level due to its ability for down/regulation of circulating levels of NADPH oxidase, one of the most important cellular sources of superoxide anion production. Our results are in agreement with some studies published so far (59-60). Histopathological results showed minimal changes in renal tissue, cellular swelling, vacuolation, desquamation, congestion and necrosis these changes involving about 50% of renal tubules, indicating the influence of rosuvastatin treatment against amikacin induced nephrotoxicity.

Effect of combination drugs against amikacin induced nephrotoxicity

In combination group, the important results from present study were the synergism between melatonin and rosuvastatin when given to animals. The combination group showed significantly more reduction in kidney weight, biochemical parameters (serum levels of creatinine, urea), inflammatory parameter (TNF-α), oxidative stress parameter (tissue MDA) and the scores of histopathological changes and elevation in the activity of antioxidant parameter (SOD) when compared with amikacin group (all tables 1, 2, 3, 4). Furthermore, the combination group showed better amelioration effect in all parameters of the present study than either melatonin or rosuvastatin groups when being given separately. The reasonable explanations for this synergistic effect could be due to the concomitant effort of the different mechanisms of action of both melatonin and rosuvastatin because of antioxidant and anti-inflammatory properties.

Conclusion

From the result of presented study, it could be concluded that the treatment of rats with melatonin and rosuvastatin inhibit amikacin-induced nephrotoxicity, and it seems that melatonin can induced this effect more than rosuvastatin. Combination of melatonin and rosuvastatin in amikacin treated rats resulted in a marked decline in kidney weight and serum urea, creatinine, TNF-α and renal MDA levels and also significant elevation in serum SOD activity. These results suggested that the protective effect of melatonin and rosuvastatin may be caused by their antioxidant and anti-inflammatory properties.

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