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LABORATORY STUDY

The impact of alpha-lipoic acid on amikacin-induced nephrotoxicity

Halil Asci¹, Mustafa Saygin², Fatma Nihan Cankara¹, Dilek Bayram³, Sukriye Yesilot¹, Ibrahim Aydin Candan³, and Ilter Ilhan⁴¹Department of Pharmacology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey, ²Department of Physiology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey, ³Department of Histology and Embryology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey, and ⁴Department of Biochemistry, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey**Abstract**

Amikacin (AK) is an antibacterial drug, but it has remarkable nephrotoxic and ototoxic side effects due to increase in reactive oxygen radicals. This study was established to determine the possible protective effects of alpha-lipoic acid (ALA), a powerful antioxidant, on AK-induced nephrotoxicity. Three different groups of rats ($n=6$) were administered saline (control), AK (1.2 g/kg, intraperitoneally), ALA (100 mg/kg, p.o.) and AK combination (ALA one day before the AK for five days). Renal function, oxidative stress markers and histological changes were evaluated at the end of the experiment. Malondialdehyde was increased as an indicator of free radical formation in AK-induced group and decreased with ALA treatment. While catalase activity was increased significantly, superoxide dismutase and glutathione peroxidase activities were not statistically significant increased with ALA treatment. The result showed that AK enhanced levels of urea, creatinine and blood urea nitrogen in serum significantly. Administration of ALA reduced these levels of biochemical markers. Histopathological observations were confirmed by biochemical findings. In conclusion, ALA is suggested to be a potential candidate to ameliorate AK-induced nephrotoxicity.

Keywords

Amikacin, alpha lipoic acid, nephrotoxicity, oxidative damage, renal failure

HistoryReceived 15 March 2014
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Published online 8 October 2014**Introduction**

Aminoglycoside antibiotics are used in several infections; including Gram-negative aerob bacteria and Gram-positive *Staphylococcus aureus*. They have beneficial effects such as wide antibacterial efficacy and low cost.¹ Aminoglycosides are bactericidal as a result of inhibition of protein synthesis and changed integrity of the bacterial cell membrane.² Amikacin (AK) is a semi-synthetic derivative of aminoglycosides. It is obtained by acetylation from a natural medicine of the kanamycin and resistant to bacterial enzymes that inactivate natural aminoglycosides. Therefore, it is the most broad-spectrum among aminoglycoside antibiotics.³ Because of these features, they are more preferred. The most important and critical side effect of AK is dose-dependent and reversible nephrotoxicity that restrains the treatment of patients. Recent studies demonstrate that reactive oxygen species have a role in the pathogenesis of AK nephrotoxicity.^{4,5} Alpha-lipoic acid (ALA) is a naturally occurring dithiol compound that functions as an essential cofactor for mitochondrial enzymes.⁶ When applied regularly, ALA accumulates in tissues and is converted to dihydrolipoic acid (DHLA) by lipoamide dehydrogenase. In recent studies, both ALA and DHLA

were found biologically active.⁷ ALA reduced superoxide radicals by metal-chelating activity and regenerated other natural antioxidants, such as vitamin C or vitamin E from their radical or inactive forms. Recently, ALA was suggested as an effective antioxidant and has been reported to protect against various drug-induced toxicities.^{8–12} This study was established to evaluate the possible renoprotective effect of ALA *via* its antioxidant properties in rats with AK-induced nephrotoxicity. The investigation was performed using histopathological changes and biochemical parameters; including malondialdehyde (MDA), serum urea, blood urea nitrogen (BUN) and serum creatinine (Cr), which are used to observe the development and extent of renal tubular damage in rats due to oxidative stress. Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) are antioxidant enzymes that prevent the tissues from oxidative damage. These enzyme activities must be increased in antioxidant treatment groups.

Materials and methods**Experimental conditions**

Female Wistar rats weighing 250–300 g were placed in a temperature- ($21 \pm 2^\circ\text{C}$) and humidity-controlled ($60 \pm 5\%$) room in which a 12:12 h light:dark cycle was maintained. The rats were distributed into three groups ($n=6$): (1) control group, which was applied saline oral gavage for five days;

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(2) AK group, injected intraperitoneally (i.p.) with 1.2 g/kg AK (Amikozit 500 mg flk, Eczacıbası Corp, Istanbul, Turkey) in a single dose;¹³ (3) AK + ALA group, injected i.p. single dose of 1.2 g/kg AK plus 100 mg/kg oral gavage ALA (Thioctazid 600 mg tab, Meda Pharma, Istanbul, Turkey) one day before the AK for five days.¹⁴ Twenty-four hours after the last administrated dose of ALA, at the end of the experiment, the blood sample was collected, both kidneys were quickly removed under 90 mg/kg ketamine (Alfamin, Alfasan IBV) and 10 mg/kg xylazine (Alfazin, Alfasan IBV) anesthesia and divided equally into two longitudinal sections. One half was placed in formaldehyde solution for routine histopathological examination by light microscopy. The other half of the kidney tissue was homogenized and kept at -80°C for biochemical evaluations (MDA, SOD, CAT, GPx). Blood samples were extracted to determine the serum levels of urea, BUN and Cr. All experiments in this study were performed in accordance with the guidelines for animal research from the National Institutes of Health and were approved by the Committee on Animal Research at Suleyman Demirel University, Isparta (15/08/2013-04).

The preparation of the tissue samples and biochemical analysis

At the end of five days, all groups were decapitated under anesthesia (ketamine HCl 90 mg/kg + xylazine HCl 10 mg/kg). For biochemical analyses, tissue samples from the kidney were collected. Kidney tissues were homogenized in a motor-driven tissue homogenizer (IKA Ultra-Turrax T25 Basic; Labortechnik, Staufen, Germany) with phosphate buffer (pH 7.4). Unbroken cells, cell debris and nuclei were sedimented by centrifugation at 10,000 g for 10 min. The levels of protein, MDA, and the activities of SOD, GPx, and CAT were determined in the supernatants. Determination of SOD activity was estimated in the supernatant according to the method described by Sun et al.,¹⁵ and its activity is expressed as units per milligram protein. Determination of GPx activity was based on the method of Paglia and Valentine, and its activity is expressed as units per milligram protein.¹⁶ CAT activity was measured using the method described by Aebi and is expressed as kilo units per gram protein.¹⁷ Protein levels in the homogenate and supernatant were determined according to the method of Bradford.¹⁸ The MDA levels in tissues were determined from the homogenate by following the double heating method of Drapper and Hadley.¹⁹ The concentration of MDA is expressed as micromoles per gram protein ($\mu\text{mol}/\text{mg}$ protein) in the kidney. An autoanalyzer (Olympus AU 2700, Melville, NY) was used to determine the activities of SOD, and a spectrophotometry (Shimadzu UV-1601; Shimadzu, Kyoto,

Japan) was used to estimate the activity of GPx, CAT and levels of MDA.

Histological determination

Right kidneys were removed from each rat and divided into the lobes after cleaning. The lobes were fixed in 10% neutral buffered formalin and embedded in paraffin. The paraffin-embedded blocks were cut to 4–5 μm and stained with hematoxylin and eosin. The slides were then examined using a light microscope (Olympus BX50) and photographed. All histological evaluations were made twice under blind conditions (without knowledge of the treatment) and histological changes were scored as follows:

- (0) score (negative score): no structural damage
- (1) score (one positive score): minimal damage
- (2) score (two positive scores): middle damage
- (3) score (three positive scores): severe damage according to research article of Abdel-Wahhab et al.²⁰

Statistical analysis

For statistical analysis, normality was investigated, and it was shown that some values of the parameters did not fit to the normal distribution. Therefore, as stated by Abdel-Wahhab et al.,²⁰ considering the small number of cases, non-parametric Kruskal–Wallis test, Mann–Whitney *U* test and chi-square test were used to compare groups. Differences were considered as significant for $p < 0.05$. All results are expressed as mean \pm SEM.

Results

MDA, SOD, CAT, and GPx in the kidney

There were statistically significant differences between all groups ($p < 0.05$). MDA levels, the marker of oxidative damage in kidney tissue, were enhanced in AK group compared to the control group, but it was not significant. In ALA-treated group, MDA levels were significantly reduced compared to the AK group ($p < 0.05$). In the antioxidant enzymes, SOD and CAT activities were significantly decreased in AK group compared with control group ($p < 0.001$ and $p < 0.05$, respectively), and only CAT

Table 2. Serum renal function tests.

Groups	BUN (mg/dL)	Creatinin (mg/dL)	Urea (mg/dL)
Control	15.50 \pm 1.04	0.57 \pm 0.07	34.97 \pm 3.26
Amikacin	24.20 \pm 7.04 ^a	0.89 \pm 0.27 ^a	52.19 \pm 15.04 ^a
Amikacin + ALA	13.80 \pm 4.96 ^b	0.57 \pm 0.15 ^b	29.44 \pm 10.75 ^b

Notes: ^a $p < 0.05$ versus control group.

^b $p < 0.05$ versus AK.

Table 1. The biochemical markers of oxidative stress.

Groups	MDA ($\mu\text{mol}/\text{mg}$ protein)	CAT (ku/mg protein)	SOD (U/mg protein)	GPx (IU/L protein)
Control	2.19 \pm 0.15	0.020 \pm 0.004	0.060 \pm 0.010	5.594 \pm 1.61
Amikacin	2.51 \pm 0.36	0.011 \pm 0.003 ^a	0.020 \pm 0.008 ^a	5.590 \pm 1.57
Amikacin + ALA	1.97 \pm 0.35 ^b	0.015 \pm 0.006 ^b	0.051 \pm 0.007	5.710 \pm 0.88

Notes: ^a $p < 0.05$ versus control group.

^b $p < 0.05$ versus AK.

Table 3. Histopathological analysis of kidneys.

	Control (n=6)				Amikacin ^a (n=6)				Amikacin + ALA ^b (n=6)			
	0	1	2	3	0	1	2	3	0	1	2	3
Glomerular congestion	6	0	0	0	0	0	2	4	0	5	1	0
Mononuclear cell infiltration	5	1	0	0	0	3	3	0	0	4	2	0
Tubular dilatation	4	2	0	0	0	0	4	2	0	4	2	0
Cortical and medullary hemorrhage	6	0	0	0	0	0	5	1	0	5	1	0
Tubular degeneration	5	1	0	0	0	0	4	2	0	4	2	0

Notes: ^aAmikacin increased renal injury, $p < 0.05$ versus control.

^bALA reduced renal injury, $p < 0.05$ versus amikacin.

The bold numbers show rating of histological changes: (0) score, no structural damage; (1) score, minimal damage; (2) score, middle damage; and (3) score, severe damage.

The light color numbers show the number of groups (0–6).

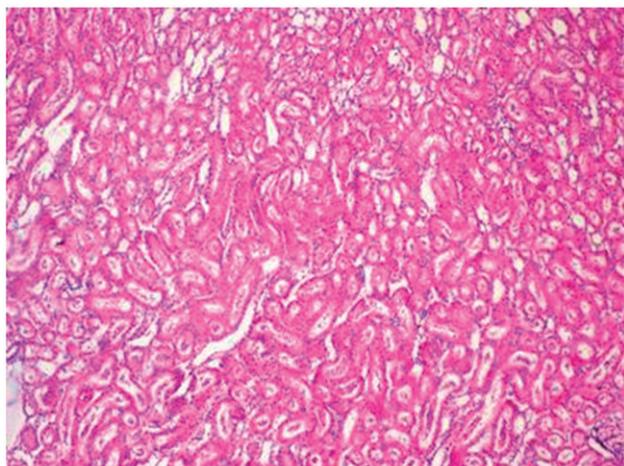


Figure 1. Control group. Kidney tissues were normal in control ($\times 10$).

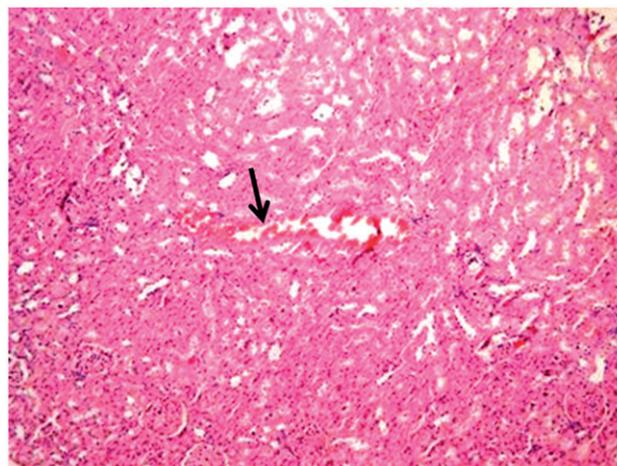


Figure 3. Amikacin group. Vascular congestion (arrow) ($\times 10$).

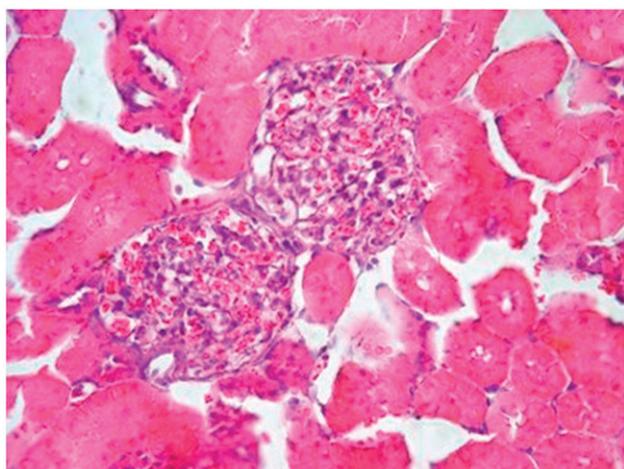


Figure 2. Control group. Kidney tissues were normal in control ($\times 40$).

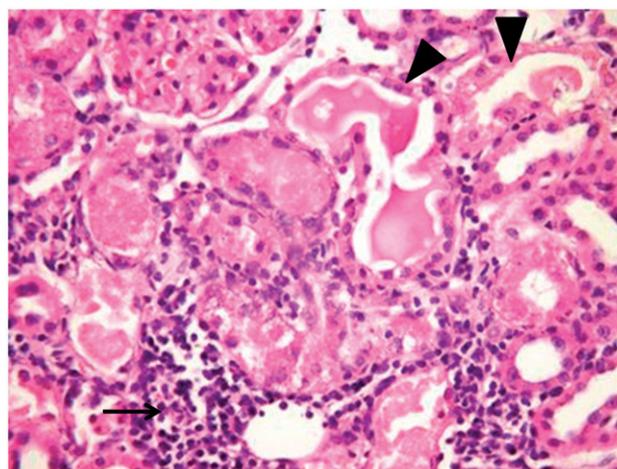


Figure 4. Amikacin group. Mononuclear cell infiltration (arrow), tubular dilatation and congestion (arrow head) ($\times 40$).

activity increased in ALA-treated group compared with the AK group significantly ($p < 0.001$). There was no significant improvement in GPx antioxidant enzyme measurements (Table 1).

Renal function test

Serum urea, BUN and Cr levels were significantly ($p < 0.05$) increased in the AK group compared to the control group (Table 2). Elevations were significantly reduced in ALA treatment compared to AK group ($p < 0.05$).

Histopathological changes

In the evaluation of the kidney tissue sections of control group, there were no histopathological findings observed under the light microscope (Table 3) (Figures 1 and 2). Glomerular congestion, mononuclear cell infiltration, tubular dilatation, cortical and medullary vascular congestion, proximal and distal tubular degeneration were observed to be statistically significant in AK-administrated group compared with the control group ($p < 0.05$) (Figures 3 and 4).

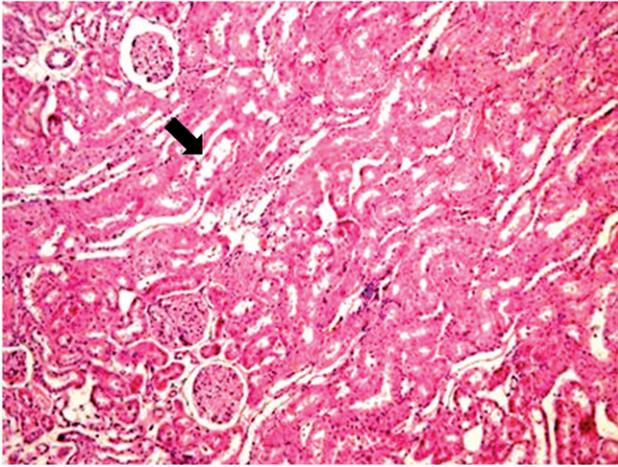


Figure 5. Amikacin + alpha lipoic acid group. Tubular dilatation (arrow) ($\times 10$).

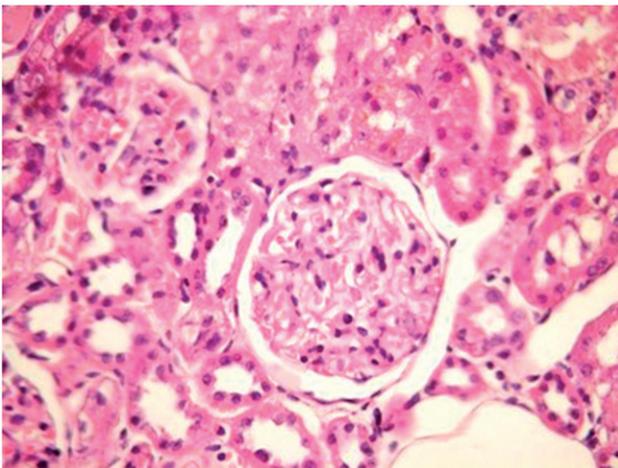


Figure 6. Amikacin + alpha lipoic acid group ($\times 40$).

ALA treatment in AK-induced kidney damage, histopathological findings, including especially tubular dilatation, cortex and medulla hemorrhage and proximal and distal tubular degeneration were decreased significantly ($p < 0.05$) (Figures 5 and 6).

Discussion

Aminoglycoside antibiotics are widely used potent bactericidal drugs. However, nephrotoxicity side effect *via* oxidant injury limits their effectiveness. The evidence of AK-induced renal damage was demonstrated in several experiments with oxidative stress mechanism in rats.^{4,5,13,14,21}

ALA is widely used as a therapeutic agent for the treatment or prevention of diabetes complications, including polyneuropathy, cataract and nephropathies.^{22–24} Nowadays, in several studies, antioxidant properties of ALA have been working mainly.^{9,14,25–28} In addition, ALA contains lipophilic and hydrophilic portions so it has lipophilic and hydrophilic properties, it also removes free radicals, regenerate other antioxidants, connect and facilitate the excretion of heavy metals. It stands out with all of these effects among other major antioxidants.^{6,29} Chloroquine-induced oxidative

damage in kidney ameliorated by the antioxidant properties of ALA at orally 100 mg/kg when compared with other doses (10 and 30 mg/kg).¹⁴ This study was designed to check the protective effect of ALA on AK-induced nephrotoxicity at a dose of 100 mg/kg.

ROS can induce lipid peroxidation in the tissues, leading the production of MDA as an indicator of increased lipid peroxidation and tissue damage.³⁰ In this study, AK administration to rats increased MDA levels and ALA treatment significantly decreased MDA production compared with the AK group.

Some studies indicated that superoxide radicals can inhibit GPx³¹ and CAT activities,³² and singlet oxygen and peroxy radicals can inhibit SOD and CAT activities.³³ The cisplatin-induced toxicity in mice exhibited a significant elevation in MDA accompanying with a significant depletion of CAT, SOD and GPx. ALA may play a renoprotective role on cisplatin-induced nephrotoxicity through antioxidant and antiapoptotic mechanisms combined with the onset of mRNA expression of antioxidant genes.²⁶ In our study, SOD and CAT activities were significantly decreased in AK group compared with the control group; SOD and CAT activities were increased in ALA-treated group compared with AK group, but only CAT activity was statistically significant. There was no significant improvement in GPx activity.

In our study, only AK-induced group increased the level of Cr, urea and BUN (renal damage indicators). Elevations were significantly reduced in ALA-treated group compared to AK group. Nephrotoxicity was manifested by a significant increase in urea and Cr resulted from reduction of glomerular filtration.³⁴ These results are in agreement with the previous reports on AK-induced nephrotoxicity.^{4,35}

Aminoglycosides are excreted from renal proximal tubules cells confirmed that aminoglycosides can induce both proximal and distal renal tubular dysfunction by using proton nuclear magnetic resonance spectroscopy of urine.^{22,36} Histopathological studies strongly support the concept that tubular necrosis is the primary cause of functional toxicity.^{5,30,35} In this study, biochemical findings were confirmed by histopathological observation. The AK-applied group showed the highest lesions scores of glomerular congestion, mononuclear cell infiltration, tubular dilatation, cortical and medullary hemorrhage, proximal and distal tubular degeneration, which indicate renal tissue damage. This could be due to the formation of highly reactive radicals as a consequence of oxidative stress caused by the AK. All these changes histopathologically reduced in ALA group. The lower cellular infiltration and lower tissue damage in ALA treatment might be associated with its antioxidant properties.^{9,26,27} These properties were important in its protective effect against oxidative renal damage.

Recent findings indicate that ALA, an antioxidant, exerts a protective role against the development of diabetic nephropathy, and the underlying mechanism may involve effective suppression of the generation of oxidants, reduction of BUN and Cr.^{29,37} Wongmekiat et al. demonstrated that ALA supplementation attenuates renal injury in rats with obstructive nephropathy with its beneficial antioxidant properties.²⁴ In another study, ALA improves both renal dysfunction, decrease abnormal levels of MDA and GSH during rat renal

ischemia/re-perfusion and all of these supported with immunohistochemistry.³⁸

In conclusion, according to our results, ALA is a powerful antioxidant agent responsible for reducing the levels of MDA, BUN, Cr and increasing antioxidant parameters, which are the indicators of the damage occurring in the kidney. Based on biochemical and histopathological determinations, ALA efficiently ameliorated AK-induced nephrotoxicity and protects kidney tissues by regenerating renal function and balancing the oxidant–antioxidant status. We thought that ALA, used in routine treatment of diabetic complications, especially neuropathy and nephropathy, would have a new indication such as treatment or prophylaxis of aminoglycoside-induced nephrotoxicity. Depending on our results, we suggest that clinicians could consider the administration of ALA during AK therapy.

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Declaration of interest

There was no source of funding for the research. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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