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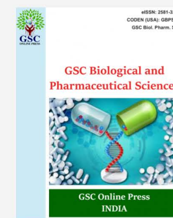

(RESEARCH ARTICLE)

Effect of coenzyme Q10 and vitamin E on gentamicin-induced nephrotoxicity in rats

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Abstract

Background/Aim: Gentamicin is an aminoglycoside antibiotic that can cause nephrotoxicity by damaging the kidneys due to high relative blood flow. In this study, the protective and therapeutic effects of CoQ_{10} and vitamin E on GM-induced nephrotoxicity were investigated.

Methods: Fifty Wistar Albino rats were used as live material in this study, which were randomly divided into 5 groups of 10 animals. These groups, and the treatment they received, were as follows: a) control group: Physiological saline (i.p) for 8 days, b) GM group: Gentamycin 80 mg/kg/day/i.p for 8 days, c) GM+CoQ10 group: Gentamycin 80 mg/kg/day/i.p+ CoQ10 10 mg/kg/day/ i.p for 8 days, d) GM+ Vit E group: Gentamycin 80 mg/kg/day/i.p+ Vit E 250 mg/kg /day/ip administrated for 8 days, and e) GM+CoQ10+Vit E group: Gentamycin 80 mg/kg/day/ip + CoQ10 10 mg/kg/day/ip + Vitamin E 250 mg/kg /day/ip for 8 days. Following the test period, urea, creatinine, K, Na, Cl, retinol, vitamin D, and vitamin E levels of the subjects were measured in plasma, while MDA, GSH, AOPP, nitrite, nitrates, CAT, SOD, and GPx activities were measured in kidney tissues.

Results: A severe nephrotoxic effect of GM administration in rats were detected as part of this study. The administration of CoQ_{10} and vitamin E, alone or in combination, was not sufficient to repair the kidney damage at the histopathological level. However, the renal tissue enzyme levels, along with other related to oxidative stress and plasma biochemical parameter analyses, were found to have improved greatly with the administration of vitamin E.

Conclusion: CoQ_{10} and vitamin E can be suggested as supplementary agents to gentamicin treatment to prevent cell degeneration in the kidney and ensure healing

Keywords: Antioxidants; Coenzyme Q_{10}; Gentamycin; Nephrotoxicity; Oxidative stress; Vitamin E

1. Introduction

The kidney is a vital organ that plays important role in the biological health, development, and growth of mammals. Antibiotics are drugs that are widely used, both in clinics and by outpatients, to treat infections. Gentamicin (GM) is an aminoglycoside antibiotic which, despite its possible nephrotoxic side effects, remains a relevant drug for Gram-negative infections and is widely used to treat a variety of bacterial infections. However, its high efficiency, preferred properties, and synergy effect with b-lactam antibiotics make it a preferred drug. Despite being well tolerated, the harmful dose-dependent and idiosyncratic side effects are well documented. Persistent nephrotoxicity is the major

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disadvantage of the clinical application of aminoglycoside antibiotics, which can trigger acute kidney failure [1]. Recent literature elucidates the underlying mechanism of gentamicin nephrotoxicity. While glomeruli remove GM by filtration, it is specifically reabsorbed from the proximal tubules. The nephrotoxic properties of gentamicin are related to accumulation in the convoluted proximal tubules of the kidney, along with a number of morphological, metabolic, and functional changes that involve radical oxygen species (ROS) [2]. ROS formed by gentamicin stimulation is the essential mediator of the nephrotoxic effect [3]. ROS are shown to be the cause of cell death in many different pathological conditions including glomerular diseases and renal ischemia-reperfusion injuries. It has been reported that GM increases renal mitochondria production of hydrogen peroxide [4] and free oxygen radicals [5]. Lipid peroxidation also increases during GM nephrotoxicity [6]. Considering this, the use of certain antioxidant substances to prevent or ameliorate the nephrotoxicity induced by GM has been investigated in literature [7-9].

Vitamin E acts as a peroxyl radical scavenger and a chain-breaker antioxidant. Vitamin E affects oxidative changes in cell organelles and prevents lipid peroxidation and cell destruction [10]. Coenzyme Q (CoQ), which structurally contains a benzoquinone ring and a polyisoprenoid tail, is widely found in every cell membrane in eukaryotic organisms and is found at varying levels in different tissues. It is also involved in the steps of ATP production in the electron transfer system, which makes it an essential substance (11).

There is no study regarding the protective roles of CoQ_{10} and vitamin E combination on nephrotoxicity induced by GM. The present study will investigate possible protective or curative effects of CoQ_{10} and vitamin E on nephrotoxicity induced by GM in rats.

2. Material and methods

2.1. Live material and experimental stage

The experimental procedures were performed according to the ethical conditions confirmed by the Ethic Committee of Yuzuncu Yil University Experimental Animal Teaching and Researcher Center (No: 26.05.2011 2011–05-16). In this study, 50 male Wistar Albino rats weighing 250-300 g live weight were used. The test animals were fed ad libitum with a standard rat diet and water for 12 hours at 24 ± 3 ° C in a ventilated room. The animals were randomly assigned into 5 groups of 10 animals. In the groups, the number of samples was changed to accommodate the analysis techniques and to obtain the required amount of samples for the technique.

- Control group: Physiological saline (i.p.) was given for 8 days.
- GM group: Gentamycin was given at 80 mg / kg / day / i.p for 8 days.
- GM+CoQ10 group: Gentamycin 80 mg / kg / day / i.p + CoQ10 10 mg / kg / day / i.p 8 days.
- GM+Vit E group: Gentamycin 80 mg / kg / day / i.p + Vitamin E 250 mg / kg / day / i.p 8 days.
- GM+CoQ10+Vit E group: Gentamycin 80 mg / kg / day / i.p + CoQ10 10 mg / kg / day / i.p + Vitamin E 250 mg / kg / day / i.p 8 days.

Ketamine (90 mg/kg) was injected intraperitoneally to anesthetize the animals, and blood samples were taken directly from the hearts of the animals 24 hours after the last GM injection. The blood was transferred to the anticoagulant tubes. Blood samples were centrifuged to separate the plasma. Urea, creatinine, Na, Cl, and K levels were measured with a Vetscan commercial kit in plasma. Plasma retinol, vitamin E and vitamin D levels were determined by HPLC [10, 12, 13]. Animals were then killed, after which both kidneys were immediately removed and washed with cold physiological saline. The samples were stored at -80 ° C until further analysis.

At the time of analysis, the frozen kidneys were thawed, and the capsules were separated and homogenized. Homogenization was performed in a homogenizer with a buffer containing 1.15% KCI [1:10 (w / v)]. Tissue homogenates were prepared at 14.000 rpm for 15 minutes at + 4 ° C to determine CAT activities with MDA, GSH, AOPP, nitrite, and nitrate levels, and at 18.000 rpm to determine GPx and SOD activities at +4°C. Renal tissue MDA [14, 15], GSH [16, 17], AOPP [18], nitrite and nitrate levels [19], CAT [20], GPx (Commercial Randox-Ransel Kit) and SOD (Commercial Randox-Ransod Kit) activities were measured by spectrophotometry. Total protein levels of renal tissue samples were also measured spectrophotometrically, using the biuret method [21].

2.2. Histopathological analysis

Tissue samples were prepared in 10 % formaldehyde for histopathologic examinations, which were microscopically stained with Van Gieson and Mallory's triple staining techniques.

2.3. Statistical analysis

Descriptive statistics for the biochemical properties under consideration were expressed as mean (SD). Differences between the means of the data were examined by Post-Hoc Duncan test. Statistical significance level was taken as P-values < 0.05 in the calculations and SPSS 13.0 package program was used for these statistical analyses.

3. Results

The mean values of MDA, GSH, AOPP, nitrite, and nitrate levels and CAT, SOD, and GPx activities of the kidney tissues belonging to control and the other four groups are provided in Table 1.

The mean values of plasma urea, creatinine, K, Na, Cl, retinol, vitamin D, and vitamin E levels of control and the other four groups are given in Table 2.

Table 1 Kidney tissue MDA, GSH, AOPP, Nitrite, Nitrate levels and CAT, SOD, GPx activities of all groups (Mean ±Sx)

	n	MDA (nmol/g tissue)	GSH (µmol/g tissue)	AOPP (µmol/g protein)	Nitrite (µmol/g tissue)	Nitrate (µmol/g tissue)	CAT (kU/g protein)	SOD (U/mg protein)	GPx (U/mg protein)
Control	7	28.0 (4.3)^{b}	32.8 (2.0)^{a}	207.8 (16.0)^{b}	29.9 (2.6)^{b}	185.8 (21.4)^{b}	9.5 (1.0)^{a}	33.6 (1.8)^{a}	35.1 (2.4)^{a}
GM	7	48.5 (2.7)^{a}	23.2 (0.9)^{c}	278.1 (24.1)^{a}	57.2 (4.4)^{a}	269.9 (29.4)^{a}	4.4 (0.4)^{b}	16.9 (1.3)^{c}	14.5 (1.8)^{d}
GM+CoQ$_{10}$	7	45.4 (3.1)^{a}	28.1(1.6)^{b}	233.9 (23.1)^{ab}	53.6 (4.8)^{a}	221.7 (10.1)^{ab}	5.1 (0.9)^{b}	25.6 (2.8)^{b}	19.6 (1.3)^{cd}
GM+Vit E	7	33.9 (1.3)^{b}	26.1(1.6)^{bc}	214.8 (15.7)^{b}	32.7 (4.1)^{b}	199.3 (17.5)^{b}	8.9 (0.6)^{a}	32.0 (1.9)^{ab}	24.1 (2.4)^{bc}
GM+CoQ$_{10}$+ Vit E	7	31.2 (4.3)^{b}	26.5 (1.1)^{bc}	227.0 (4.9)^{ab}	46.1 (3.9)^{a}	223.5 (12.0)^{ab}	7.4 (0.6)^{a}	25.4 (3.2)^{b}	27.7 (1.2)^{b}
P		**	***	**	**	**	**	***	***

**P < 0.01, ***P < 0.001; a,b,c,d The difference between the means shown with different letters in each column is statistically significant (Post-Hoc Duncan test P < 0.05), n: number of samples.

Table 2 The mean values of plasma urea, creatinine, K, Na, Cl, retinol, vitamin D and vitamin E levels of control and the other four groups (Mean ±Sx)

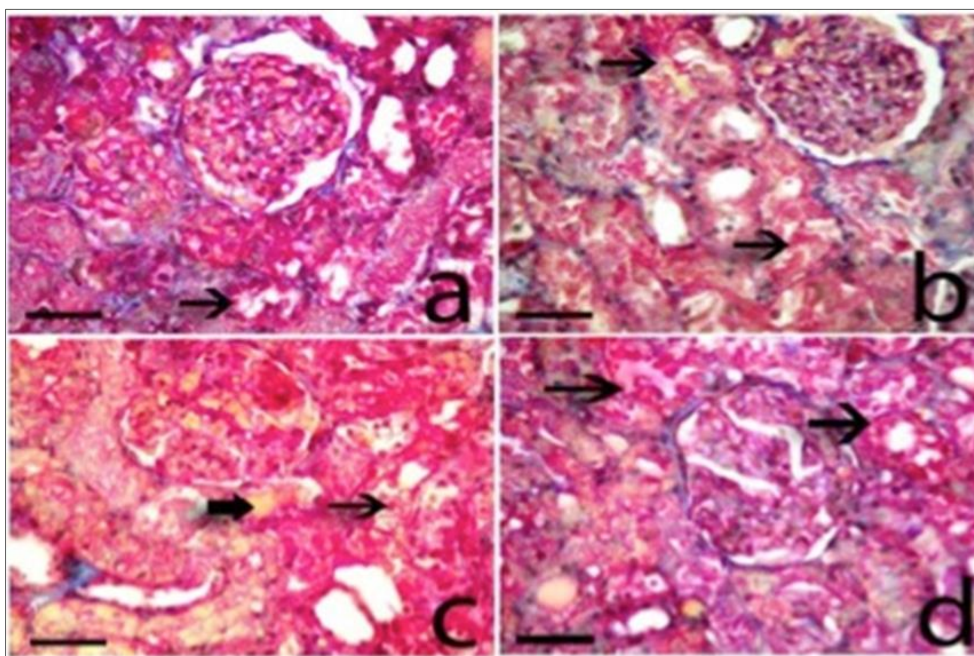
	n	Urea (mg/dl)	Creatinine (mg/dl)	K (mmol/L)	Na (mmol/L)	Cl (mmol/L)	n	Retinol (µg /ml)	Vitamin D (µg /ml)	Vitamin E (µg /ml)
Control	7	59.0 (2.6)^{c}	0.5 (0.1)^{c}	3.8 (0.2)^{a}	137.7 (1.7)^{ab}	109.2 (1.7)^{a}	7	0.2 (0.0)^{b}	0.03 (0.0)^{a}	1.8 (0.3)^{b}
GM	7	323.6 (36.0)^{a}	4.1 (0.4)^{ab}	2.7 (0.1)^{c}	131.1 (1.9)^{dc}	94.4 (2.2)^{c}	7	0.3 (0.0)^{a}	0.04 (0.0)^{a}	2.0 (0.3)^{b}
GM+CoQ$_{10}$	7	263.1 (32.0)^{ab}	2.8 (0.6)^{b}	3.7 (0.2)^{a}	135.1 (0.8)^{bc}	103.0 (3.1)^{ab}	5	0.3 (0.1)^{a}	0.04 (0.0)^{a}	2.3 (0.3)^{b}
GM+Vit E	7	190.0 (15.4)^{b}	3.4 (0.5)^{ab}	2.9 (0.2)^{bc}	130.7 (1.3)^{d}	97.3 (1.3)^{bc}	6	0.3 (0.0)^{a}	0.03 (0.0)^{a}	4.1 (0.5)^{a}
GM+CoQ$_{10}$+ Vit E	7	282.4 (32.4)^{a}	4.5 (0.4)^{a}	3.4 (0.2)^{ab}	140.7 (1.6)^{a}	103.9 (1.9)^{a}	5	0.3 (0.0)^{a}	0.04 (0.0)^{a}	3.8 (0.4)^{a}
P		***	***	***	***	***		**	*	**

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; ^{a,b,c,d} The difference between the means shown with different letters in each column is statistically significant (Post-Hoc Duncan test $P < 0.05$), n: number of samples.

The levels of vitamins (retinol ($P < 0.01$), vitamin D ($P < 0.05$) and vitamin E ($P < 0.01$)), and urea, creatinine, K, Na, and Cl ($P < 0.001$) levels against certain biochemical nephrotoxicity parameters induced by GM, are provided in Table 2. Inspection of Table 2 as a whole reveals a slight increase in retinol ($P < 0.01$) and vitamin D values ($P < 0.05$) following GM injection. Plasma vitamin E levels can be seen to have increased from 2.0 µg/ml to 2.3 µg/ml in GM and GM+CoQ$_{10}$ groups, but vitamin E levels increased significantly after injection in the vitamin E supplementation groups ($P < 0.01$). LPO ($P < 0.01$) and CAT ($P < 0.01$), GSH level, SOD, and GPx activities ($P < 0.01$) in the tissues are also better in the GM+Vit E group, indicating that the increase in vitamin E levels results in an antioxidant capacity magnifying effect.

Here, tissue and plasma changes are also supporting each other. Vitamin E levels can be observed to have decreased from 4.1 µg/ml to 3.8 µg/ml, while retinol and vitamin D values in the GM+CoQ_{10}+Vit E group show insignificant changes compared to the GM+Vit E group.

Histopathological examinations were performed on the kidney tissues of all groups. Degeneration and necrosis in the proximal tubules was the most prominent finding in the kidney sections of rats receiving gentamicin. Some tubulous epithelial cells were found to have bulbous and blurred cytoplasm due to parenchymal degeneration, while vacuoles associated with vacuolar degeneration were seen in many tubule epithelia (Figure 1). Necrotic tubules were more common in the majority of the sections examined. Most of the tubule epithelium was completely necrotic and the nuclei disappeared, while lumen depletion was also observed as necrotic pink masses. It was noticed that the nuclei of the few epithelial cells that were partially intact were picnotic. Necrosis tubules were found to be more intense in the cortex and increased in severity toward the outer part. No histopathological differences in the severity of necrosis and degeneration was observed between the GM-alone treated rats and the treatment groups and no regenerated tubules and mitosis were observed (Figure 1).



a: GM group, arrow: necrosis and degeneration in the proximal tubule, b: GM+CoQ_{10} group arrows: necrosis and degeneration in the proximal tubule, c: GM+Vit E group, thin arrow: necrosis and degeneration in the proximal tubule, thick arrow: necrotic structures, d: GM+CoQ_{10}+Vit E group, arrows: necrotic and vacuolar proximal tubules. Triple staining, bar = 35 µm

Figure 1 Histopathological examinations were performed on the kidney tissues of all groups

4. Discussion

Aminoglycosides show their effects rapidly and have high antibacterial activities. They are cost-effective antibiotics that are frequently used in gram (-) bacteria infections [22]. Their use is largely limited, however, due to their side effects, especially their nephrotoxicity. Among the factors that influence the nephrotoxic effects of aminoglycosides are factors such as duration of treatment, genetic predisposition, dose of the drug, and patient age. There are many studies in the literature investigating the nephrotoxicity caused by aminoglycosides [23, 24].

GM is excreted by the kidney through glomerular filtration without being metabolized in the body, but it is partially reabsorbed in the proximal tubule cells. This causes some accumulation of GM, which is found only in lysosomes in proximal tubule cells.

Aminoglycosides also cause renal vasoconstriction with thromboxane B2 and cause direct cellular toxicity, especially in the proximal tubule, which absorbs and stores drugs in the lysosome. Thus, tubular necrosis, tubular atrophy, intertubular myeloid bodies, and interstitial nephritis may develop [24]. Reactive oxygen species are probably responsible for proximal tubular necrosis and acute renal failure caused by GM. ROS also causes peroxidation of membrane lipids, breakdown of polyunsaturated fatty acids, and release of various aldehydes and alkenes during

oxidative stress. This release may intensify the release and formation of molecular oxygen (O2-) from free radicals due to GM.

It is known whether oxidation in membranes, tissues, and biomolecules due to free radicals play an important role in pathological cases. It is known, however, that the interaction of free oxygen radicals produced in large amounts with biomolecules (nucleic acids, lipids, polysaccharides, and various proteins) causes cell and tissue damage. The free radicals produced damage the base membranes of the kidney glomeruli, impair tubule functions, and break down collagens and other matrix components. Moreover, when free oxygen radicals are formed in the environment, lipid peroxidation follows, which changes the permeability and fluidity of the cell membrane. MDA can be used as a marker of oxidative damage during lipid peroxidation [25].

Experimental studies using GM have shown that lipid peroxidation and MDA levels increase due to free radical formation. In the study of Walker et al., it was reported that gentamicin caused iron release and production of reactive oxygen species from the kidney cortical mitochondria, thus leading to the development of oxidative stress [3].

Glutathione, which prevents or reduces the destructive effects of free radicals. It acts as a substrate for peroxidases and transferases. Glutathione protects biological membranes against lipid peroxidation. This protection occurs enzymatically. Glutathione peroxidase (GSH-Px) for the activity of glutathione turns the reduced form (GSH) into the reduced state (GSSG). Glutathione can also react with many harmful oxidants such as hydroxyl radicals and superoxide anion without enzyme catalysis [26]. Free radical damage seems to play an important role in the pathogenesis of GM-induced nephrotoxicity. Although there are different results in studies, generally a decrease in enzymatic antioxidant (glutathione, SOD, CAT, etc.) levels have been observed in oxidative damage. In some studies, it was determined that the level of glutathione decreased in rats treated with GM [27, 28].

CoQ10 is not only an important component in the mitochondrial respiratory chain but also a naturally occurring hydrophobic component that exhibits potent antioxidant properties. CoQ10 is used in the treatment of oxidative damage and disorders caused by insufficient cellular energy metabolism [29]. It was observed that CoQ10 abolished the production of reactive oxygen species by the expression of NADPH oxidase [30]. Researchers found that CoQ10 scavenges lipid peroxidation products during the reactions of free radicals [31] and that CoQ10 also suppressed nitrate tissue stress and nitric oxide products [32]. Upaganlawar et al. found that serum urea and creatinine levels, which increased as a result of nephrotoxicity, decreased significantly when CoQ10 was administered with GM. In the same study, they found that when CoQ10 was given with GM, the increased MDA level decreased due to nephrotoxicity and free radical formation, and the decreased glutathione level increased [28]. In another study, it was observed that CoQ10 administration significantly suppressed lipid peroxidation and repaired antioxidant defense mechanisms against the nephrotoxicity of cisplatin, an aminoglycoside [33].

It has been reported that very positive results are obtained if Coenzyme Q treatment is administered before the nephron epithelium is impaired in individuals with functional disorders in their kidneys [34]. In the case of additional CoQ administration, the different responses detected in different tissues of the organism have been the most preoccupying issue for scientists in recent years. In other words, its widespread presence in tissues does not mean that perfect results will be obtained with the addition of CoQ in correcting every pathology. It has been emphasized that the CoQ supplement given for kidney treatment might be bad for some other pathological disorders, and different results have been obtained while researching its potential benefits [35].

Recently, advanced oxidation protein products, a new marker of protein oxidation, have begun to attract the attention of various researchers [36]. Protein oxidation is defined as the covalent modification of proteins that are indirectly formed by sequential products of reactive or oxidative stress with reactive oxygen metabolites. In the present study, tissue levels of AOPP, nitrate, and nitrite were also found to have increased in the GM group, supporting a moderate but positive approach to control values GM+Vit E. When these three parameters are examined, it is found that GM+Vit E yields better results than GM+CoQ10+Vit E in preventing renal nephrotoxicity. The lowest values in all three parameters were observed in the GM+Vit E group, and it can be said that this result should be considered the correct method, eventhough the histopathological data does not accompany the improvements.

In the present study, MDA levels, were 28.03 nmol/g tissue at controls, which increased to 48.46 nmol/g following GM treatment. GSH level and CAT, SOD, and GPx activities were significantly decreased due to the suppressive effect of GM. These values reveal GM's damaging effect on the kidney through ROS. These results are consistent with Priyamvada et al. and show how toxic GM is for the kidney [37]. This issue should be taken seriously as increasing the enzyme levels of food supplements and antioxidant substances given will trigger biochemical changes that will end up reducing LPO. CoQ10 and vitamin E in this study were administered to reduce the damage caused by ROS. CoQ10 applications, which

were started with GM injection, had beneficial effects on MDA, GSH levels, and CAT, SOD, and GPx activity in the tissues, but these values were still close to the GM group.

As a result of the investigation, it seems that CoQ10 alone can not suppress the damage done by GM. However, in the group given vitamin E, there are obvious increases in CAT, SOD, and GPx values, while MDA, GSH, and AOPP drop considerably. These results are better compared to that of CoQ10 alone. This suggests that vitamin E is a better antioxidant than CoQ10 in GM nephrotoxicity. When CoQ10 and vitamin E were given together, the observed MDA levels were close to the control values. In CAT and SOD, there was a lower activity in GM+CoQ10+Vit E than in the GM+Vit E group. The expected improvement in the GM+CoQ10+Vit E group was not fully formed. The presence of oxidants still indicates the presence of destruction in the kidney. Histopathological findings show that although the biochemical values are partially improved at the end of the experiment, there are still ongoing healing and damage processes in the kidney. However, according to biochemical tissue analysis, it is possible that increasing the duration of treatment can return the kidney to normal again.

Findings such as decreased glomerular filtration and an increase in serum creatinine and urea values are interpreted as nephrotoxicity. GM-induced nephrotoxicity includes pathologies such as acute tubular necrosis, renal failure, and renal concentration impairment, which results from its accumulation in the renal cortex [38, 39]. When chronic or acute kidney failure occurs, the end products of nitrogen metabolism accumulate in the body, and the levels of non-protein nitrogenous substances increase. This leads to an increase in serum urea and creatinine levels. An indicator of kidney damage after GM ingestion is an increase in serum urea and creatinine values, which are markers of glomerular damage [39, 40]. In experimental studies in which GM was applied, it was reported that typical nephrotoxicity findings emerged with protein excretion in the urine and a significant increase in serum creatinine and urea. It was also reported that GM causes tubular necrosis and renal atrophy develops. Increases in urea and creatinine levels in all of these studies were associated with GM-induced nephrotoxicity. GM administration resulted in decreased MDH, ICDH, G6Pase, and FBPase, and an increase in serum BUN, creatinine, proteinuria, glucosuria, phosphaturia, and LDH, G6PDH activity. This symbolizes the transformation of aerobic to anaerobic energy metabolism, demonstrating mitochondrial deterioration [41].

Accordingly, it was concluded that GM application caused a severe nephrotoxic effect in rats which caused profound damage to necrosis, some tubular epithelial cells appeared to have a swollen and cloudy cytoplasm due to parenchymal degeneration, many tubular epithelia had vacuoles associated with vacuolar degeneration. Severe kidney damage and biochemical changes were also observed in this study. The short-term positive effect of CoQ10 and vitamin E alone or in combination on GM nephrotoxicity was not found at the histopathological level but positive changes were found in the renal tissue enzymatic analyzes, indicators of oxidative stress, and plasma biochemicals. Lipid peroxidation and antioxidant enzyme levels were positively altered with the addition of CoQ10 and vitamin E, giving the appearance of supporting substances for future clinical applications. However, according to the results obtained in this study, it can be suggested that CoQ10 and vitamin E should be administered together for longer periods to prevent cell degeneration in the kidney and ensure healing.

In the present study, it was shown through biochemical marker values that Vit E and CoQ10 had a curative effect against GM nephrotoxicity.

5. Conclusion

In summary, this study shows that CoQ_{10} and vitamin E help against GM-induced nephrotoxicity, possibly by reducing lipid peroxidation due to GM and showing a protective effect. These agents also provide a certain level of biochemical protection against all types of oxidative damage. In the clinical use of GM as an antibacterial drug, co-administration of vitamin E and CoQ_{10} may offer an alternative to prevent nephrotoxic side effects.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

Handan Mert, Nihat Mert, Mecit Yörük, Ibrahim Hakki Yoruk, Betul Apaydin Yildirim and Halil Cumhur Yilmaz declare that they have no conflict of interest. All institutional and national guidelines for the care and use of laboratory animals were followed.

Statement of ethical approval

The ethical approval is obtained from Yuzuncu Yil University Animal Researches Ethic Committee in the session held on 26.05.2011(decision number 2011.05.16).

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