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Research Article
Effect of Thiamine Pyrophosphate on Amiodarone-Induced Oxidative Kidney Damage in Rats

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Abstract

Background and Objective: Amiodarone-induced kidney damage is associated with an increase in oxidant and proinflammatory cytokines. This study was planned to investigate the effect of thiamine pyrophosphate (TPP) on amiodarone-induced oxidative and inflammatory kidney damage in rats on both a biochemical and histopathological basis. **Materials and Methods:** Albino Wistar-type male rats (6 rats per group) were divided into healthy (HG), amiodarone (ADG) and amiodarone+TPP (TAG) groups. The TPP (20 mg kg^{-1}) and amiodarone (50 mg kg^{-1}) treatment continued for 14 days. Analyzes of oxidant, antioxidant and proinflammatory cytokines in excised kidney tissues and creatinine and blood urea nitrogen in serum were performed. **Results:** The amiodarone treated rats showed an increase in malondialdehyde, tumor necrosis factor, interleukin 1 beta, interleukin 6 levels, serum creatinine and blood urea nitrogen in the kidney tissue while a decrease was observed in total glutathione as compared to healthy animals ($p<0.001$). In addition, histopathological damage occurred in the kidney tissues of the ADG group. It was determined that TPP prevented biochemical changes and histopathological damage significantly ($p<0.001$). **Conclusion:** By acting as an antioxidant and anti-inflammatory, TPP might protect kidney tissue from amiodarone-induced damage.

Key words: Amiodarone, antioxidant, free oxygen radicals, kidney, oxidative damage, thiamine pyrophosphate, rat

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Amiodarone is an antiarrhythmic drug of class III. Amiodarone has been approved for the treatment of ventricular arrhythmias by the United States Food and Drug Administration (FDA). The drug is, however, usually prescribed for the treatment of supraventricular tachyarrhythmias[1,2]. The distinguishing feature of amiodarone over other antiarrhythmics of class III is that it also inhibits beta-adrenergic receptors as well as calcium and sodium channels[3]. It is unfortunate that undesirable side effects may develop during the course of treatment with amiodarone. There has been evidence that amiodarone has predominantly adverse effects on the thyroid, pulmonary and cardiac systems[4], however, sometimes serious side effects may cause the treatment to be terminated[5]. There is evidence in the literature that amiodarone can induce Alström syndrome (blindness, decreased hearing, obesity, type-2 diabetes, dilated cardiomyopathy, liver and kidney dysfunction) in the human body[6]. Furthermore, liver and kidney failure have been reported following the administration of amiodarone[7]. Nevertheless, amiodarone has been shown to have a more severe toxicity on kidney cells than on hepatocytes[2]. Free oxygen radicals (ROS) have been assumed to be produced during the metabolism of amiodarone and are involved in the mechanism behind some of its side effects[8]. Previously, an increase in oxidant and proinflammatory cytokines has been associated with kidney damage induced by amiodarone[9]. This evidence from the literature suggests that antioxidants and anti-inflammatory drugs may be effective for treating kidney damage caused by amiodarone[7].

The active metabolite of thiamine, thiamine pyrophosphate (TPP)[10], is known to have antioxidant and anti-inflammatory effects[11]. It has also been demonstrated experimentally that TPP protects kidney tissues as well as non-renal organ tissues from oxidative and proinflammatory damage caused by cytokines[11-14]. Based on the information reported in the literature, TPP may be effective to the treatment of kidney damage caused by oxidative stress and inflammation. The literature does not provide any information regarding the effects of TPP on kidney damage caused by amiodarone. Accordingly, this study was designed to determine the effects of TPP in amiodarone-induced oxidative and inflammatory kidney injury in rats, both by biochemical and histopathological examination.

MATERIALS AND METHODS

Study area: The current study was carried out in Erzincan Binali Yıldırım University Experimental Animals Application and Research Center in June, 2023.

Animals: Eighteen albino Wistar male rats weighing 268-280 g, purchased from Erzincan Binali Yıldırım University Experimental Animals Application and Research Center, were included in this study. For the experimental animals to adjust to their environment, they were housed and fed in groups for a week at 22±2 with 12 hrs of light and 12 hrs of darkness. The experimental procedures were performed with the approval of the Local Animal Experimentation Ethics Committee (Date: 27-04-2023, meeting/decision no: 4/14).

Chemical substances: Among the drugs used in this experiment, thiopental sodium was obtained from Ibrahim Etem Ulagay (Turkey), TPP from Biofarma (Russia) and Amiodarone (200 mg tablet) from Sanofi Pharmaceutical Industry (Turkey).

Experimental animal groups: Albino Wistar-type male rats (6 rats per group) were randomly assigned to the healthy (HG), amiodarone-treated (ADG) and amiodarone+TPP-treated (TAG) groups.

Experiment procedure: An injected dose of TPP of 20 mg kg^{-1} was administered intraperitoneally (ip) to TAG animals. An equal volume of distilled water was applied ip to the HG and ADG. One hour after applications the TAG and ADG groups were administered amiodarone 50 mg kg^{-1} by gavage. For a period of 14 days, this procedure was repeated once a day. Subsequently, the animals were euthanized by administering thiopental (50 mg kg^{-1}) and kidney tissues were removed. To evaluate the oxidant level in kidney tissues, malondialdehyde (MDA) and to evaluate the antioxidant status, total Glutathione (tGSH) level and superoxide dismutase (SOD) and catalase (CAT) activities were measured. Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1β (IL-1β) and Interleukin-6 (IL-6) levels were determined to assess the inflammation status. In addition, the histological structures of the kidneys were examined. Before euthanasia, creatinine and blood urea nitrogen (BUN) analysis were performed on blood samples taken from the tail veins. All data were evaluated by comparing between groups.

Biochemical analyses

MDA, tGSH, SOD, CAT and protein determination: Tissue samples were first washed with 0.9% NaCl and then homogenized by adding liquid nitrogen. The supernatant formed after centrifugation was used for analysis. The amounts of MDA (item No: 10009055), GSH (item No: 703002) and SOD (item No: 706002) in kidney tissues were analyzed using commercial ELISA rat kits (Cayman Chemical Company).

Kit instructions were followed for measurements. The analysis of CAT was performed using the method proposed by Góth[15]. The Bradford method was used to determine protein concentration by spectrophotometry at 595 nm[16].

TNF-α, IL-1β and IL-6 analysis: Kidney tissues were homogenized by treatment with liquid nitrogen. The PBS (pH 7.4) was added 1/10 (w/v) and centrifuged at 10000×g for 20 min. The supernatant portion was used in the analysis. The TNF-α, IL-1β and IL-6 analysis were performed according to commercial rat kits instructions (Eastbiopharm Co. Ltd., ELISA kit, China).

Creatinine measurement: According to the Moore method[17], spectrophotometric method was used to determine serum creatinine quantitatively on a Roche brand Cobas 8000 autoanalyzer.

BUN measurement: An autoanalyzer of the Roche brand Cobas 8000 was used for the quantitative determination of serum urea levels using a spectrophotometric method[18]. It was calculated with the formula:

$$\text{Blood urea nitrogen} = \text{Urea} \times 0.48$$

Histopathology analysis: Kidney tissue samples were fixed in 10% formaldehyde (72 hrs) and subsequently they were washed (24 hrs). Then, consecutive series of alcohols were used for dehydration. Samples passed through xylol were placed in paraffin wax. Sections of 4-5 μm were taken from the obtained blocks and the hematoxylin-eosin (H&E) procedure was administered. Sections were evaluated using the DP2-SAL firmware program and a light microscope (Olympus Inc., Tokyo, Japan). For each sample, five peripheral and one central area were selected from serial sections and semi-quantitative scoring was performed on the selected areas. There were several histopathological changes in kidney tissue, including glomerular degeneration, tubular vacuolization, tubular necrosis, congestion and interstitial connective tissue accumulation. The samples were scored according to each criterion as follows: 0: normal, 1: Mild damage, 2: Moderate damage and 3: Severe damage. A pathologist who was blinded to the experimental groups performed the histopathological assessment and scoring.

Statistical analyses: The "SPSS for Windows, 22.0" statistical program was used for all statistical operations. The graphics were created using GraphPad Prism 9.0.0. Based on the Shapiro-Wilk Test, which determined that the data were normally distributed, one-way ANOVA was used for statistical analysis. In light of the fact that the variances were homogeneously distributed according to the Levene test results, Tukey HSD was preferred as a *post hoc* Test. The biochemical data were expressed as "Mean+Standard Error" (X±SEM). Kruskal-Wallis Test was used for ordinal histopathological data and Dunn test was used for group comparisons. Histopathological data were presented as median (Q1-Q3). A $p<0.05$ value was determined for statistical significance.

RESULTS

MDA, tGSH, SOD and CAT analysis results: As seen in Table 1 and Fig. 1a, the MDA value in the kidney tissues of the amiodarone group (3.38±0.09) was significantly higher than the healthy animals (1.67±0.07) ($p<0.001$). There was an inhibition of this increase in the TAG group (1.87±0.12) ($p<0.001$). On the basis of MDA values, there was no difference between HG and TAG ($p = 0.308$).

Table 1: Analysis results of biochemical data obtained from experimental groups

	Experimental group			Pairwise comparison			
Biochemical parameter	HG	ADG	TAG	HG vs ADG	HG vs TAG	ADG vs TAG	F/p
MDA	1.67±0.07	3.38±0.09	1.87±0.12	<0.001	0.308	<0.001	102.333/<0.001
tGSH	4.48±0.11	2.42±0.09	3.72±0.06	<0.001	<0.001	<0.001	139.338/<0.001
SOD	8.35±0.11	4.27±0.09	7.43±0.09	<0.001	<0.001	<0.001	490.842/<0.001
CAT	6.23±0.11	3.32±0.10	5.72±0.06	<0.001	0.002	<0.001	307.054/<0.001
TNF-α	2.51±0.08	5.41±0.18	3.26±0.05	<0.001	0.001	<0.001	175.917/<0.001
IL-1β	3.42±0.08	5.73±0.06	3.74±0.08	<0.001	0.017	<0.001	300.825/<0.001
IL-6	2.24±0.04	4.82±0.04	2.62±0.05	<0.001	<0.001	<0.001	1136.105/<0.001
Creatinine	1.11±0.03	2.23±0.09	1.24±0.04	<0.001	0.045	<0.001	112.585/<0.001
BUN	44.00±1.71	143.67±2.01	51.00±1.86	<0.001	0.302	<0.001	888.968/<0.001

MDA: Malondialdehyde, tGSH: Total Glutathione, SOD: Superoxide dismutase, CAT: Catalase, TNF-α: Tumor Necrosis Factor-alpha, IL-1β: Interleukin 1 beta, IL-6: Interleukin 6, BUN: Blood urea nitrogen, HG: Healthy group, ADG: Amiodarone applied group, TAG: Thiamine pyrophosphate+amiodarone applied group. Statistical analysis was done with the one way ANOVA test, then Tukey's Test was applied. The results are presented as the Mean±standard error. A $p<0.05$ value was determined for statistical significance

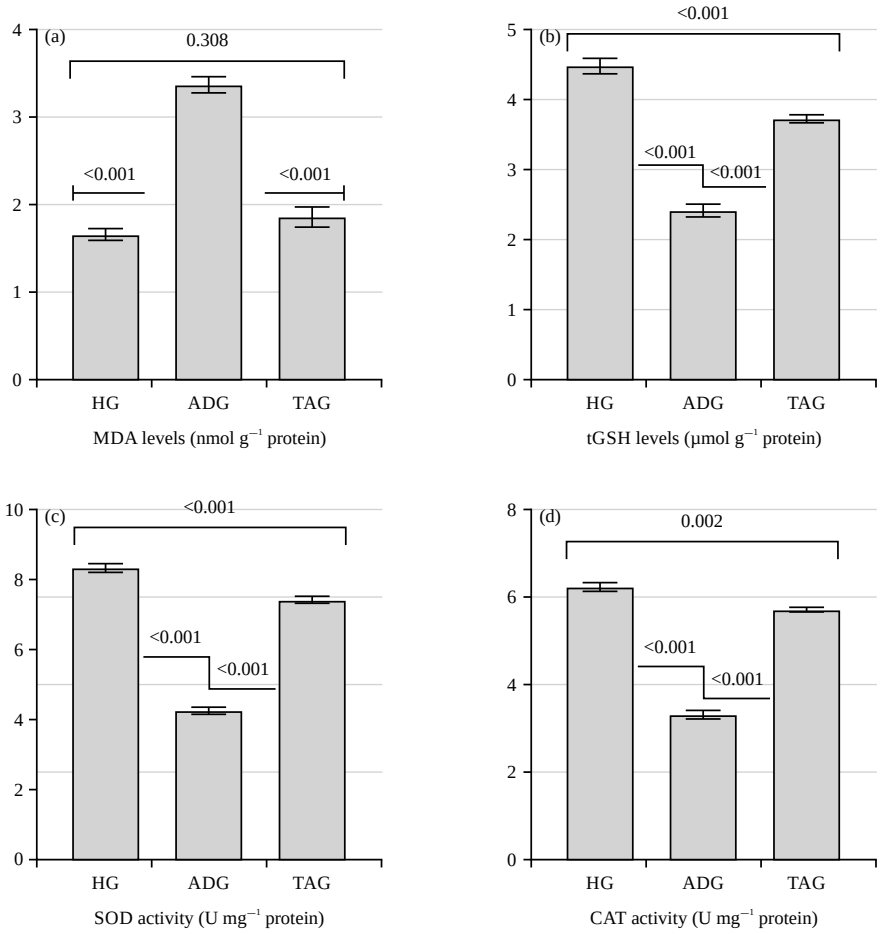

Fig. 1(a-d): Analysis results of (a) MDA, (b) tGSH, (c) SOD and (d) CAT data obtained from experimental groups

Bars show X±SEM, n = 6. MDA: Malondialdehyde, tGSH: Total Glutathione, SOD: Superoxide dismutase, CAT: Catalase, HG: Healthy group, ADG: Amiodarone applied group, TAG: Thiamine pyrophosphate+amiodarone applied group

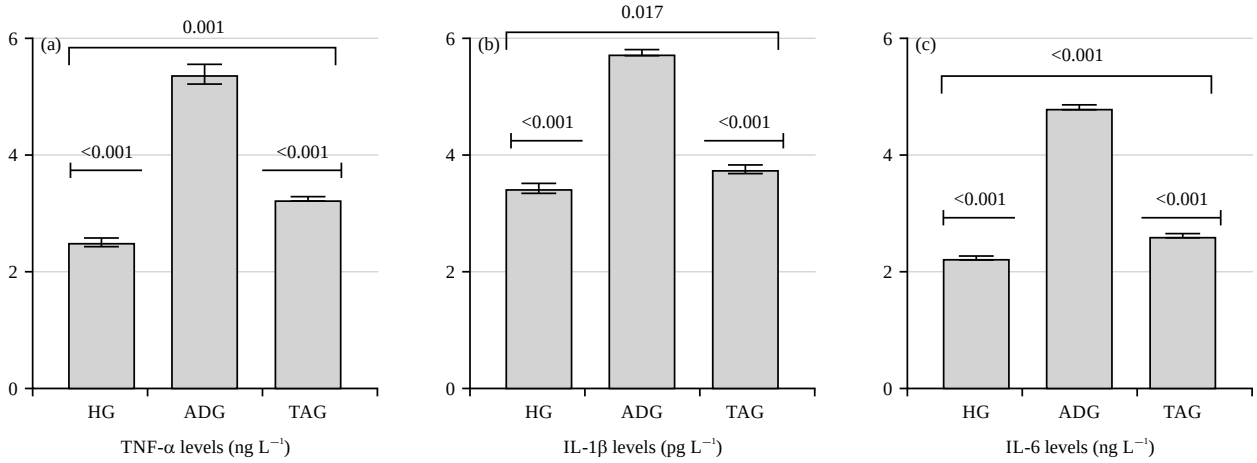

Fig. 2(a-c): Analysis results of (a) TNF-α, (b) IL-1β and (c) IL-6 data obtained from experimental groups

Bars show X±SEM, n = 6. TNF-α: Tumor Necrosis Factor-alpha, IL-1β: Interleukin 1 beta, IL-6: Interleukin 6, BUN: Blood urea nitrogen, HG: Healthy group, ADG: Amiodarone applied group, TAG: Thiamine pyrophosphate+amiodarone applied group

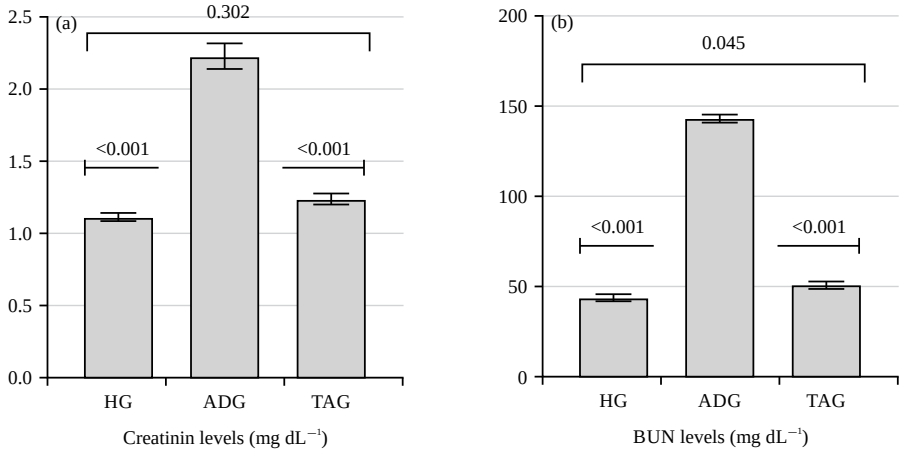

Fig. 3(a-b): Analysis results of (a) Creatinine and (b) BUN data obtained from experimental groups

Bars show X±SEM, n = 6. BUN: Blood urea nitrogen, HG: Healthy group, ADG: Amiodarone applied group, TAG: Thiamine pyrophosphate+amiodarone applied group

Antioxidant levels were also measured in kidney tissues (Table 1, Fig. 1b-d). In comparison with the HG group (4.48±0.11, 8.35±0.11 and 6.23±0.11, respectively), it was found that tGSH, SOD and CAT levels were decreased in kidney homogenates from the ADG group (2.42±0.09, 4.27±0.09 and 3.32±0.10, respectively) ($p<0.001$). The TPP (3.72±0.06, 7.43±0.09, 5.72±0.06, respectively) treatment indicated that the decrease in tGSH, SOD and CAT values was suppressed ($p<0.001$).

TNF-α, IL-1β and IL-6 analysis results: As presented in Table 1 and Fig. 2a-c, TNF-α, IL-1β and IL-6 levels in the kidney tissues of the ADG group (5.41±0.18, 5.73±0.06 and 4.82±0.04, respectively) with increased oxidant and antioxidants levels were found higher than the healthy group (2.51±0.08, 3.42±0.08 and 2.24±0.04, respectively) ($p<0.001$). A significant difference was found between the TAG group (3.26±0.05, 3.74±0.08 and 2.62±0.05, respectively) and ADG group in terms of TNF-α, IL-1β and IL-6 values ($p<0.001$).

Plasma creatinine and BUN analysis results: Table 1 and Fig. 3a-b illustrated that serum creatinine and BUN levels were higher in the ADG group (2.23±0.09 and 143.67±2.01, respectively) compared to the HG group (1.11±0.03 and 44.00±1.71, respectively) ($p<0.001$). Creatinine and BUN levels in the TAG (1.24±0.04 and 51.00±1.86, respectively) were lower than in the ADG ($p<0.001$).

Histopathology findings: When the kidney tissue samples from the HG group were evaluated histopathologically, it was noted that the glomerular structures, the proximal and distal tubules and the epithelial cells of the tubules had a regular appearance. According to the findings, the capillary vascular network of the glomeruli and the border of Bowman's space were in a normal state. There were no pathological findings in the interstitial connective tissue areas or the blood vessels in these areas throughout the tissue (Fig. 4a and Table 2). It was evident from light microscopy that the kidney tissues of the ADG group had an increase in connective tissue in the interstitial area and severe congestion in the blood vessels. A significant collapse of the glomerular vascular network was observed, as well as signs of dilatation in Bowman's space. There was a significant amount of degeneration in epithelial cells of the proximal and distal tubules. The cells were determined to be separated from the basement membrane. The tubule cells were found to have vacuolized and suffered extensive necrotic damage throughout the tissue (Fig. 4b, c and Table 2). Based on the examination of kidney tissues of the TAG group, it was determined that the borders of the glomerular capillary network were regular, similar to those of the healthy group. The dilatation in Bowman's space was significantly reduced compared to the damage group and it was similar to the health group. The presence of proximal and distal tubule cells was evident and no necrotic damage was observed. Despite the appearance of normal connective tissue in the interstitial area, mild congestion in the blood vessels persisted (Fig. 4d and Table 2).

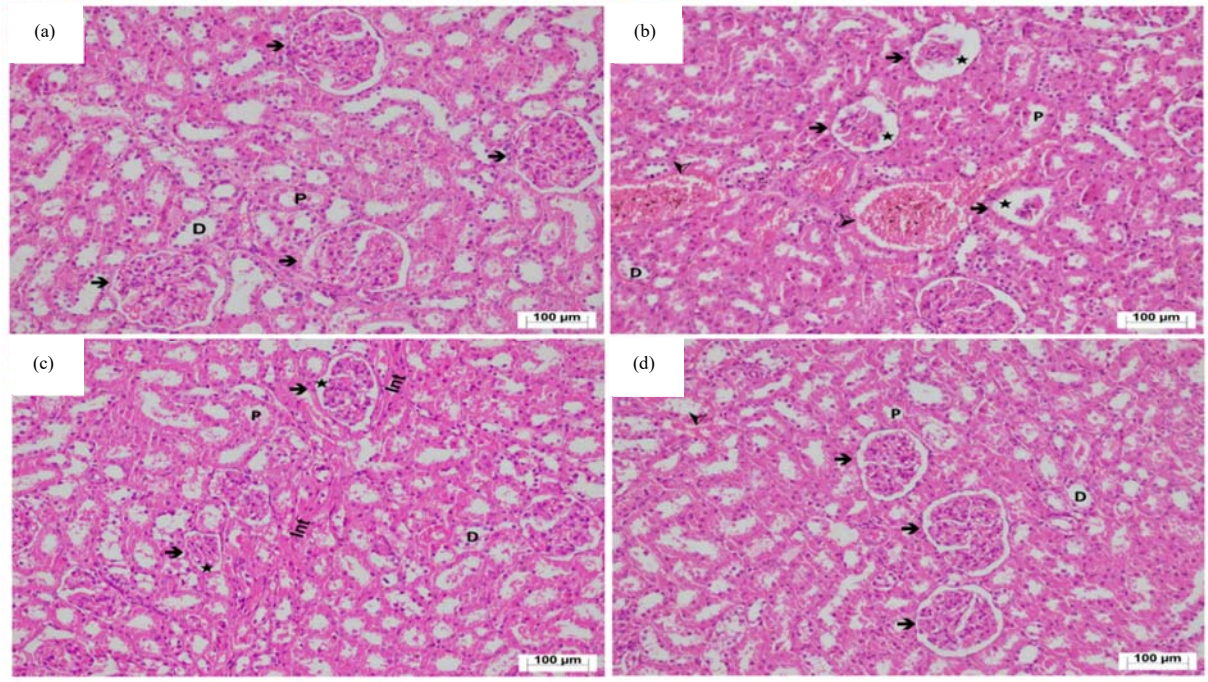

Fig. 4(a-d): Kidney tissue belonging to the (a) HG, (b) ADG, (c) ADG and (d) TAG

→: Glomeruli, P: Proximal tubule, D: Distal tubule, ★: Glomeruli dilatation-collapse capillary, ➢: Congestion, Int: Interstitial tissue increase and H&E×200

Table 2: Analysis results of histopathological data obtained from experimental groups

	Experimental group			Pairwise comparison			
Histopathological parameter	HG	ADG	TAG	HG vs ADG	HG vs TAG	ADG vs TAG	H/p
Glomerular degeneration	0(0-0)	3(2-3)	0(0-1)	<0.001	0.056	<0.001	89.795/<0.001
Tubular vacuolization	0(0-0)	3(2-3)	0(0-1)	<0.001	0.079	<0.001	90.312/<0.001
Tubular necrosis	0(0-0)	3(2-3)	0(0-0.75)	<0.001	0.512	<0.001	92.022/<0.001
Congestion	0(0-0)	3(2-3)	1(0-1)	<0.001	0.009	<0.001	90.536/<0.001
Interstitial tissue increase	0(0-0)	3(3-3)	0(0-1)	<0.001	0.157	<0.001	90.268/<0.001

0-3: 0: Normal, 1: Mild damage, 2: Moderate damage, 3: Severe damage. HG: Healthy group, ADG: Amiodarone applied group, TAG: Thiamine pyrophosphate+amiodarone applied group. Statistical analysis was done with the Kruskal-Wallis test, then Dunn's Test was applied. The results are presented as the median (Q1-Q3). A $p<0.05$ value was determined for statistical significance

DISCUSSION

Amiodarone is an anti-arrhythmic drug that is frequently used in the prevention and treatment of various arrhythmias. However, it has been reported in the literature that amiodarone has a high toxicity profile, as well as severe side effects affecting multiple organs[19]. In this study, the protective effect of TPP in a rat model of amiodarone-induced nephrotoxicity was investigated biochemically and histopathologically. Experimental results revealed that, while increasing MDA, TNF-α, IL-1β and IL-6 values in rat kidney tissues, amiodarone decreased tGSH, SOD and CAT levels and caused an increase in serum BUN and creatinine levels. According to the results of histopathological analysis, amiodarone caused tissue damage to the kidneys. Amiodarone-induced biochemical and histopathological abnormalities were significantly suppressed in the rat group treated with TPP.

Oxidative stress due to increased ROS was attributed to amiodarone's renal toxicity[9,20]. While ROS in small concentrations were necessary for cellular activity, their uncontrolled accumulation led to chain reactions that damaged cellular macromolecules (such as protein, lipid and nucleic acid). The current study suggested that cell membrane lipids were exposed to ROS attacks as a result of an increase in MDA in the kidney tissues of the amiodarone group[21]. The MDA was one of the end products of lipid peroxidation and was frequently used to determine whether or not oxidative stress was experienced[22]. In their studies, Eid *et al.*[9] and Fattiny and Al-Amri[20] also found that amiodarone increased MDA

levels in rat kidney tissues. However, TPP, when combined with amiodarone, was found to be effective in maintaining MDA levels at the same level as the healthy group. In addition to being the active metabolite of thiamine, TPP also played a significant role in regulating cellular redox levels[12]. Previous studies revealed that TPP protected membrane lipids from ROS attacks[11]. Altuner *et al.*[12] also found that TPP prevented the increase in MDA induced by oxidative kidney damage induced by ischemia and reperfusion.

Increased levels of oxidants in oxidative stress are associated with an increase in antioxidant depletion[23,24]. Therefore, the amount of tGSH in the kidney tissues of the animals has also been measured. The GSH is a tripeptide found extensively in many tissues, containing cysteine, glycine and glutamic acid[25]. The GSH acts directly with ROS to oxidize thiol groups and maintain cell integrity[11]. Intracellular GSH depletion due to increased ROS may cause tissue damage by inducing oxidative stress and apoptosis[23]. Literature searches have not revealed any studies concerning amiodarone's effects on tGSH levels in kidney tissue. However, it has been revealed experimentally that amiodarone causes a decrease in GSH levels in the lung[26] and liver[27] tissues of rats. Similar to the literature, there was a decrease in tGSH levels in the amiodarone group in this study. In the TPP group, this decrease was significantly suppressed. As known, TPP, an enzyme cofactor, increases GSH synthesis and has an antioxidative effect[11]. The TPP has been shown to prevent GSH depletion in oxidative kidney damage in an earlier experimental study[12].

The activity of SOD in kidney tissues of rats was also investigated in the current study. As an enzymatic antioxidant, SOD catalyzed the conversion of superoxide to oxygen and less toxic Hydrogen Peroxide (H_2O_2)[28]. According to the results of analysis, amiodarone was associated with a reduced SOD activity compared to the healthy group. The rat kidney was previously revealed to have lower SOD activity when amiodarone was administered[9]. Uysal *et al.*[29] however, found in a clinical study that amiodarone use at different doses did not alter SOD or CAT activity compared with control groups. In this study, CAT was evaluated as another indicator of antioxidant activity. The CAT activity was suppressed in the amiodarone group according to experimental results. Similar to current findings, Fattiny and Al-Amri[20] also found that amiodarone reduced CAT activity in kidney tissues. The CAT was a key enzyme in the detoxification of H_2O_2. As CAT activity decreased, the amount of H_2O_2 in the body increased, which caused both direct damage to cells and the Fenton reaction to damage them as well[28]. Biochemical analyses revealed that it inhibited amiodarone-induced reductions in CAT activity in the TPP group. During the literature review, no studies were found regarding the effect of TPP on SOD and CAT levels in oxidative kidney tissue. There were, however, studies which demonstrated that TPP prevented the decrease in SOD[14] and CAT[30] levels in oxidative damage induced by various factors.

In the literature, an increase in the release of proinflammatory cytokines and the role of oxidative stress in the toxicity mechanism of amiodarone have been reported[9]. According to the literature, ROS induced the secretion of inflammatory mediators such as TNF-α and IL-1β by increasing the production of NF-κB[11,31]. Furthermore, it was reported that this increase in the synthesis of proinflammatory cytokines increased ROS production and intensified damage[32]. It has been previously reported that amiodarone increased TNF-α[33] and IL-6[9] in rat kidney tissue. In a recent study, amiodarone was found to increase serum IL-1β and IL-6 levels in rats[34]. Supporting these studies, the current biochemical findings also revealed that there was a significant increase in TNF-α, IL-1β and IL-6 levels in the amiodarone group compared to the healthy group. Combining TPP with amiodarone prevented this increase by showing anti-inflammatory properties and brought TNF-α, IL-1β and IL-6 levels closer to those of the healthy group. As reported by Yadav *et al.*[35] thiamine exhibited anti-inflammatory properties by suppressing the increase in NF-kB due to oxidative stress. In the literature, there was no study carried out on the effect of TPP on TNF-α, IL-1β and IL-6 levels in oxidative kidney tissue. Experimentally, TPP was shown to inhibit the increase in the levels of TNF-α and IL-1β in oxidative ovarian damage[11]. In a study conducted on diabetic rats, it was stated that TPP inhibited the increase in serum TNF-α and IL-6 levels[36].

The serum creatinine and BUN levels, which were considered to be specific biomarkers of renal dysfunction[37], were also investigated in the current study. Serum creatinine and BUN levels were found to be higher in rats receiving amiodarone treatment than in the healthy group. It was found in a previous clinical study that patients using amiodarone had higher levels of creatinine as their blood concentrations of amiodarone increased[38]. Rats treated with amiodarone were revealed to have increased serum creatinine levels and urea levels in experimental studies[20,39]. This study found that treatment with amiodarone and TPP suppressed the increase in creatinine and BUN in the rat group. In a similar study, Mahdavifard and Nakhjavani[36] found that TPP had nephroprotective properties and prevented the accumulation of creatinine and proteinuria in rats with diabetes-related oxidative stress.

The kidney tissues obtained from the experimental groups were also histologically examined. The biochemical results were supported by the presence of severe glomerular degeneration, tubular vacuolization and necrosis, congestion and increased interstitial connective tissue in the amiodarone group. It was determined that amiodarone caused severe tubular necrosis[20], abnormal glomerular capillaries, damaged mesangial cells and impaired proximal tubules with abundant lysosomes[9] in rat kidney tissue. In contrast, TPP combined with amiodarone significantly protected kidney tissues. In the literature, no study analyzed the protective effects of TPP on the histological structure of the kidney. However, it was experimentally shown in the literature that TPP prevented ovarian tissue from cyclophosphamide damage[11] and liver tissue from propofol damage[13].

Preclinical and clinical studies indicate the toxic effect of amiodarone on various organs[4,6,20]. Thiamine is a vitamin with a short half-life and is not stored in the body. Although there is no tolerable upper intake level in thiamine treatment, there are no reports of the adverse effects of excessive thiamine intake[40]. The preventive effects of thiamine on early diabetic nephropathy have been demonstrated in clinical studies[41] and it has been stated that thiamine treatment causes improvement in left ventricular functions[42]. On the other hand, in some cases, the conversion of thiamine to active TPP is inhibited due to thiamine pyrophosphokinase deficiency[43]. Therefore, it may be considered to produce amiodarone and TPP drug combinations to reduce or eliminate the toxicity of amiodarone on multiple organs including the kidney.

The limitations of this study were that TPP is not administered in different ways and at different doses. In addition, it is important to conduct studies at the molecular level in the future to better reveal the mechanisms by which TPP acts on amiodarone-induced renal toxicity.

CONCLUSION

Amiodarone caused an increase in oxidants and kidney function tests as well as a depletion of antioxidants in the kidney tissues of rats. The increase in proinflammatory cytokines also revealed that inflammatory processes were also involved in the damage caused by amiodarone. Histopathological findings confirmed the toxic effects of amiodarone on kidney tissue. Meanwhile, TPP exhibited antioxidant and anti-inflammatory properties, protecting kidney tissue against the effects of amiodarone. For a better understanding of amiodarone's toxic effects on the kidney tissue and the mechanism of TPP's protective effects, studies at the molecular level should be conducted.

SIGNIFICANCE STATEMENT

Kidney tissue is an organ that is highly exposed to toxic substances due to its functions. Renal toxicities are frequently encountered nowadays, where chronic diseases and polypharmacy are seen intensely. Amiodarone, on the other hand, is a drug approved by the FDA and frequently included in treatment protocols. Therefore, in this study, an answer was sought to the question of whether amiodarone using TPP could be useful in the treatment of damage. The results of this study suggest that TPP can be used in the treatment of renal toxicity associated with the use of amiodarone.

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