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Research Article

Renal Protective Effect of Dexpanthenol on Doxorubicin-Induced Nephrotoxicity: An Experimental Rat Study

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Abstract

Objectives: It is a condition in which kidney damage occurs in patients receiving doxorubicin treatment and prevents the continuation of treatment. In this study, we aimed to demonstrate the preventive effect of dexpanthenol on kidney damage in rats given doxorubicin experimentally.

Methods: Thirty-two male rats (weight 250-300 g) were randomly divided into 4 groups, with 8 in each group. The control group was given 0.8 ml saline instead of doxorubicin. 2.5 mg/kg doxorubicin was given to the doxorubicin group cumulative dose of 15 mg/kg. In the doxorubicin + dexpanthenol group, 500 mg/kg dexpanthenol was applied to the left inguinal regions of the rats as i.p. every day for 14 days, and 15 mg/kg doxorubicin was applied.

Results: Kidney damage was significantly less in the group receiving dex compared to the group receiving only dox ($p<0.05$). Dexpanthenol showed this effect by reducing oxidative stress, especially Cas-3 and TNF-a values ($p<0.05$).

Conclusion: It has been shown in many studies that dexpanthenol has a protective effect against oxidative stress. However, its effect against real damage due to doxorubicin has not been studied before. Our study is important as it shows that doxorubicin-related kidney damage can be reduced with dexpanthenol.

Keywords: Dexpanthenol, doxorubicin, inflammation, nephrotoxicity, oxidative stress

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Despite advances in cancer treatments, cancer-related deaths occur frequently.[1] In addition, side effects of chemotherapeutic drugs used in cancer treatments on organs such as the kidneys are common. Although some preventive treatments are given to reduce these side effects, sufficient progress has not been made yet.

Doxorubicin (Dox), an anthracycline-derived antibiotic, is used as an effective chemotherapeutic drug for cancers.[2,3] Dox causes damage to the heart, liver, brain, and kidney tissues weeks after repeated applications.[4]

Dox targets topoisomerase II α to block DNA replication, which is highly expressed in cancer and required for cell division.[5,6] However, it creates lipid peroxidation and free oxygen radicals. As a result of research, the mechanisms responsible for nephrotoxicity largely caused by Dox appear to be as follows: Multifactorial, increased lipid peroxidation, oxidative stress, and endoplasmic reticulum-mediated apoptosis.[7] The most important factor of Dox-induced

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nephrotoxicity is oxidative stress. These free oxygen radicals contribute to nephrotoxicity by increasing the permeability of glomerular capillaries and tubular degeneration.[8]

Different antioxidant treatments have been tried to protect tissues against this negative side effect of Dox.[9-12] In this study, we planned to investigate the renal protective effect of dexpanthenol (Dex) in dox-induced nephrotoxicity. Thus, it may be possible to reduce the undesirable effects associated with Dox, which has high effectiveness in antineoplastic treatment but whose use is limited due to its side effects, especially nephrotoxicity.

Methods

Experimental Animal Protocol

The procedures were carried out by the Guideline of National Health Institutes for the Care and Use of Laboratory Animals. 32 male rats weighing between 250-300 grams were divided into 4 groups of 8 each. An ad libitum feeding regime was applied by keeping the rats in a 12-h day and 12-h night simulation at 21 - 22 °C using Euro type 4 cages. Four groups of 8 rats were determined as Dox, Dox+Dex, Dex and control groups.

Control Group

Intraperitoneal 0.8 ml of physiological saline was applied to the rats in this group every day for 14 days.

Dox Group

The rats in this group were given a total of 15mg/kg Dox intraperitoneally three times a week.[13]

Dex+Dox Group

Rats in this group were given 500 mg/kg of Dex intraperitoneally from the left inguinal region every day for 2 weeks, and a total of 15mg/kg of Dox was given intraperitoneally from the right inguinal region three times a week.

Dex Group

To the rats in this group, 500 mg/kg Dex was administered intraperitoneally every day for two weeks.[13,14]

Animals were slaughtered while under anesthesia using intramuscular 15 mg/kg xylazine and intramuscular 50 mg/kg ketamine. Kidney tissues were placed in formaldehyde (10%) for histopathological and immunohistochemical examinations and a part of kidney were transferred to Eppendorf tubes for biochemical and genetic analyzes and stored at – 80 °C.

Histopathological Assessment

Kidneys were collected and fixed in a 10% neutral formalin solution for histopathological analysis. For this reason kidney samples were routinely processed using a tissue processor (Leica, Wetzlar, Germany) and immersed in paraffin wax. A microtome was used to cut sections 5 microns thick (Leica Microsystems, Wetzlar, Germany). After, sections were processed for hematoxylin–eosin (HE) staining.

Immunohistochemical Evaluation

On slides coated with poly-L-lysine, two series of sections were cut and drawn from each kidney paraffin block. As instructed by the manufacturer, the sections were stained for caspase-3 expression (Anti-caspase-3 Antibody (E-8): sc-7272) and TNF-α expression (Anti-TNF-α Antibody (52B83): sc-52746, 1/100 dilution) (Santa Cruz, Texas, USA). Streptavidin-alkaline phosphatase conjugate and a biotinylated secondary antibody were used for immunohistochemistry on the sections after they had been incubated with the primary antibodies for 60 minutes. The EXPOSE Mouse and Rabbit Specific HRP/DAB Detection IHC kit (ab80436) from Abcam (Cambridge, UK) was utilized as a secondary antibody. Diaminobenzidine (DAB) was used as the chromogen. An antigen dilution solution was used as negative controls in place of primary antibodies. On blinded samples, a professional pathologist from a different university performed each evaluation.

Sections were inspected individually for the immunohistochemical analysis of each antibody. The degree of immunohistochemistry reactivity of cells with markers was evaluated semiquantitatively using a grading scale from (0) to (3): (0) negative, (1) focal weak staining, (2) diffuse weak staining, and (3) diffuse marked staining. Ten distinct regions were examined under 40X objective magnification for each section. Morphometric analysis and microphotography were conducted using the Database Manual Cell Sens Life Science Imaging Software System (Olympus Co., Tokyo, Japan). The results were kept after being subjected to statistics.

Biochemical Analysis

Serum urea and creatinine levels were assessed for kidney function using the Beckman Coulter AU5800 and a compatible commercial kit based on the spectrophotometric method.

The oxidant-antioxidant status in rat kidney tissues was evaluated by spectrophotometrically measuring TAS and TOS levels. Commercial kits from Rel Assay Diagnostics, Türkiye, were utilized with a Beckman Coulter AU5800 autoanalyzer. The Oxidative Stress Index (OSI) values were calculated using the formula OSI = [(TOS / TAS) × 100].[15-17]

Genetical Analysis

The isolation of RNA from kidney samples was conducted using the GeneAll-Ribospin RNA isolation kit. RNA quan-

tity and purity were assessed using the BioSpec Nanodrop device from Shimadzu Ltd. based in Kyoto, Japan. The RNA concentration for each sample was standardized to 500 ng/µl and preserved at -80 °C until further use in the cDNA synthesis phase.

For cDNA synthesis, we followed the protocol provided by the ABT cDNA Synthesis Kit. On ice, the following concentrations were prepared for each sample: 2 µl of 10X reaction buffer, 1µl of dNTP mix (2.5 mM), 2µl of random hexamer (50µM), 1µl of Reverse Transcriptase (200U/µl), 0.5µl of RNase inhibitor, 3.5 µl of RNase-free water, and 10µl of RNA sample. The prepared mixture was then placed in a thermal cycler following the kit protocol. All stages were carried out in a single cycle, and the resulting cDNAs were stored at -20°C.

Primer sequences were designed by identifying specific mRNA sequences and testing potential primer sequences using the NCBI. Expression levels were quantified using the Biorad-CFX 96 RT qPCR instrument, along with the ABT-2X qPCR SYBR Green MasterMix. RT-qPCR conditions, as per the manufacturer's instructions, involved an initial denaturation at 95 °C for 5min, followed by forty cycles of 20 second at 95 °C and 30 second at 60 °C. The G6PDH gene expression was used for normalization, and each sample was run in triplicate.

Statistical Analysis

SPSS package program (v22.00, IL, USA) was used for statistical analysis. Data was expressed as mean±standard deviation (SD) and median-interquartile range (IQR). All parameters were analyzed by appropriate post hoc tests involving ANOVA and Fisher's Least Significant Difference (LSD). For statistical analysis, scores of the groups were compared between the groups, the Oneway ANOVA Duncan test was used for this. $P<0.05$ was considered as significance.

Results

Histopathological Findings

Significant hyperemia, mild to moderate hemorrhages, tubular epithelial cell degeneration, protein droplets in the proximal tubules, tubule cystic dilatation, proteinous materials in the tubular lumens, and inflammatory cell infiltrations were all observed in kidney sections from the Dox group during the histological analysis. Dex treatment reduced pathological results in the Dox+Dex group. The Control and Dex groups had normal tissue histology (Fig. 1) The investigation's findings demonstrated that Dox damages kidneys and that Dex treatment enhanced pathological findings.

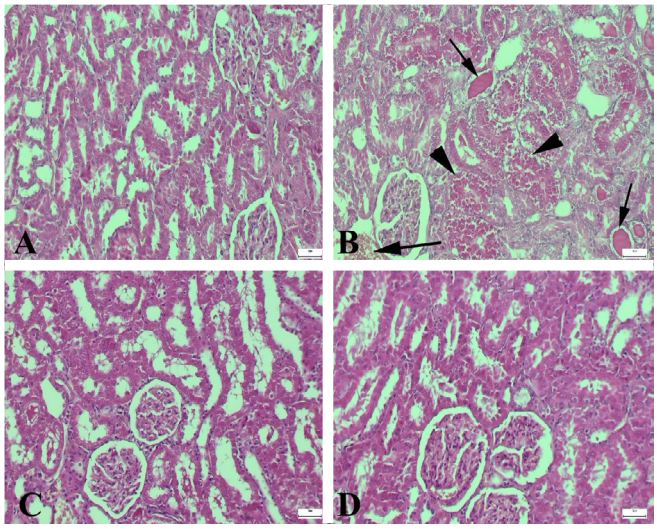

Figure 1. Microscopical appearances among the groups. **(a)** Normal tissue histoarchitecture in Control group. **(b)** Marked hemorrhage (thick arrow), proteinous materials in the tubular lumens (thin arrows) and protein droplets in the proximal tubules in the Dox group. **(c)** Deescalate pathological findings in Dox+Dex group. **(d)** Normal kidney histology in Dex group, HE, scale bars=50µm.

Immunohistochemical Findings

The immunohistochemical examination revealed elevated expressions of TNF-α and caspase-3 in tubular epithelial cells. Following Dex medication, expression was lower in the Dox+Dex group. Only very minor or unfavorable expressions were seen in the Control and Dex groups (Figs. 2, 3). Table 1 presents the statistical analysis's findings.

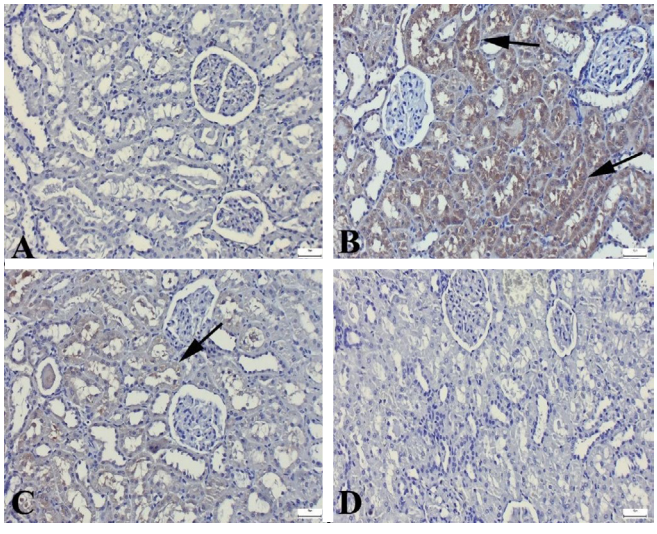

Figure 2. Caspase-3 immunohistochemical evidences between the groups. **(a)** Negative expression in Control, **(b)** Marked increase in expressions in tubular epithelial cells in Dox group, **(c)** Decreased expressions in Dox+Dex, **(d)** No expression in Dex group.

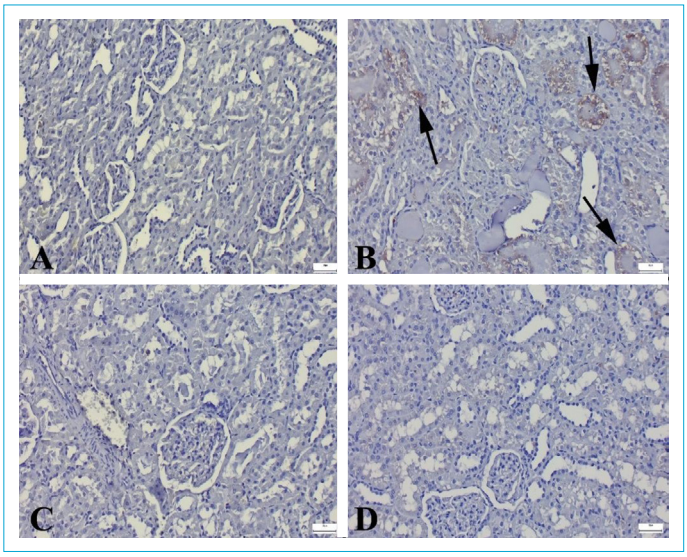

Figure 3. TNF- α immunohistochemistry results among the groups. **(a)** Negative findings in Control, **(b)** Increased findings in tubular epithelial cells, **(c)** Decreased findings in Dox+Dex, **(d)** Negative findings in Dex group.

Table 1. Immunohistochemical value between the groups.

Groups	Cas-3 Value	TNF-α Value
Control	0.25±0.16[a]	0.25±0.16[a]
Dox	2.50±0.53[b]	1.75±0.70[b]
Dox+Dex	0.75±0.31[a]	0.62±0.51[a]
Dex	0.25±0.16[a]	0.25±0.16[a]
p	<0.001	<0.001

*: The differences between the groups are statistically significant, P<0.001;
**: Data expressed mean±standard deviation.

mRNA Expression Analysis Findings

Gene expression levels related to endoplasmic reticulum (ER) stress and apoptosis were assessed across different experimental groups. The Doxorubicin (Dox) treatment group exhibited elevated expressions of Bax and Cas 9 compared to the control group. Conversely, there was a notable reduction in the expression levels of Bcl-2 and G6PDH genes in the Dox group. Remarkably, in the Dox+Dex group, where Dex was administered alongside Dox, the expression profiles of these genes were significantly altered, closely resembling those of the control group. These findings, as illustrated in Figure 4, suggest that Dex administration alleviated the ER stress induced by Dox in kidney tissue. In summary, Dex treatment appeared to mitigate the ER stress instigated by Dox, as evidenced by the restoration of gene expression patterns comparable to those observed in the control group.

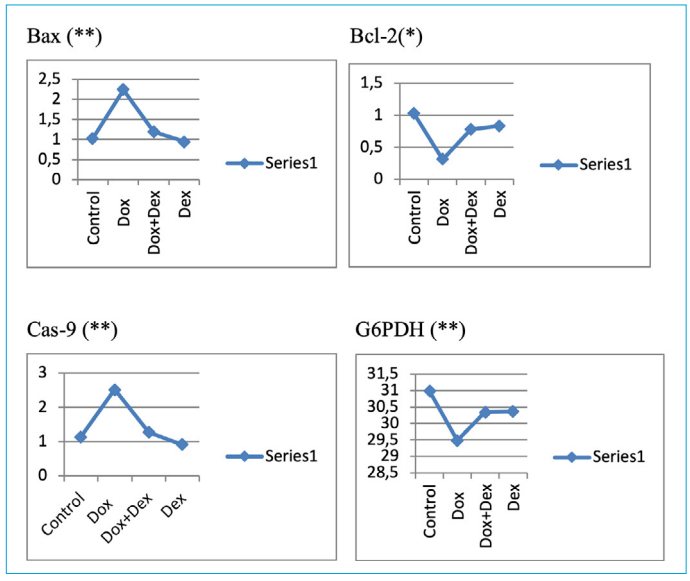

Figure 4. Assesment of relative mRNA expression in all groups. *p<0.05, **p<0.001. (G6PDH: GlycerAldehyde 3-Phosphate DeHydrogenase, BAX: Bcl-2-Associated X-protein, BCL-2: B-Cell Lymphoma 2, Cas-9: Caspase-9.)

Biochemical Analysis Findings

Notable reductions in TAS, Cr, and urea values were observed in the Dox group compared to the control group. Conversely, TOS and OSI exhibited an increase in the Dox group. In the Dox+Dex group, there was an improvement in these parameters, closely resembling levels observed in the control group (Table 2). Dex appears to effectively regulate oxidative stress induced by Dox in kidney tissue.

Table 2. Cr, Ure, TOS, OSI and TAS values between groups

	Control	Dox	Dox+Dex	Dex	p
Cr	0.2±0.03	0.4±0.03	0.3±0.04	0.2±0.02	a)<0.001 b)<0.001 c)<0.001
Ure	40.5±6.9	75.4±26.04	48.1±6.8	41.8± 5.1	a)<0.001 b)=0.03 c)<0.001
Tos	14.7±3.7	25.6±4.4	17.2±3.4	13.5± 2.6	a)<0.001 b)<0.001 c)<0.001
Tas	1.1±0.08	0.8±0.06	1.06±0.1	1.2±0.1	a)=0.01 b)=0.03 c)<0.001
Osı	1.3±0.4	2.8±0.4	1.6±0.4	1.1±0.2	a)<0.001 b)<0.001 c)<0.001

Control vs. Dox: a; Dox vs. Dox+Dex: b; Dox vs. Dex: c; Dex: dexpanthenol; TOS: total oxidant status; Dox: doxorubicin; OSI: oxidative stress index; TAS: total antioxidant status.

Discussion

Dox is an effective chemotherapeutic agent used in the treatment of many cancers.[2,3] Despite this effectiveness, it causes nephrotoxicity as a side effect. This situation may stop the administration of the drug or cause comorbidities due to side effects.[17] Many antioxidants have been tried to reduce or eliminate these effects of Dox.[18-20] In this study, we examined the effectiveness of Dex's antioxidant and anti-inflammatory properties in preventing side effects of Dox, a chemotherapeutic agent.

Studies have been published showing that Dex, a member of the vitamin B family, prevents tissue damage.[13,21,22] Dex's anti-inflammatory and antioxidant activity has also been demonstrated in many experimental studies.[23-25] A study showed that Dex improved the negative effects of gamma rays.[26] Again, in a study conducted by Tepebasi et al., it was shown that the harmful side effects of Dox were improved by using Dex.[13]

In this study conducted on rats, the damage to the kidney tissue due to Dox use was evaluated in terms of biochemical, pathological, Immunohistochemical, and genetic analysis, and the effects of Dex on these damaged tissues were revealed together with the control group. In the pathological examination of the tissues, it was shown that Dex did not have a negative effect on the kidney tissue by comparing it with the control group. However, it was observed that there was bleeding, hyperemia and degeneration of tubule cells in the kidney tissues of rats receiving Dox. Damage to renal tubule cells was decreased in the Dox+Dex group. In tubular epithelial cells, increased caspase-3 and TNF-α expressions were seen during the immunohistochemistry analysis in the Dox. Expression was reduced in the Dox+Dex after Dex therapy. In the Control and Dex, there were only very slight or negative expressions observed. These findings suggest that Dex may have renal protective effects. In biochemical parameters, the decrease in OSI, TOS, Ure, and Cr values along with Dex, the increase in TAS value, and the decrease in Bax and Cas 9 amplification in genetic analysis, as well as the increase in Bcl-2 and G6PDH values may indicate a decrease in oxidative stress in the kidneys, which may help prevent the damage caused by Dox.

This study is an experimental study aimed at reducing the nephrotoxic effect of Dex due to Dox. The fact that it is one of the first studies in this field in the literature brings our study to the fore. However, the increase in Bcl-2 and G6PDH expression due to doxorubicin administration indicates increased oxidative stress. Dex application suggests that the decrease in Bcl-2 and G6PDH expression may be attributed to the decrease in oxidative stress in the kidneys.

In our study, Dox was shown to increase ER-derived Bax, which induces apoptosis. In addition, it was observed that Bcl-2, which reduces apoptosis, decreased. It has also been shown to increase Cas-9, which is a different pathway that increases apoptosis. These indicators showed that ER-induced apoptosis and Dox damaged the tissues, and this situation was also revealed histopathologically. It has been observed that these findings also support previous studies in the literature. In a study conducted on experimental rats in which a sepsis model was created, it was shown that Dex reduced the inflammation and apoptosis caused by sepsis on tissues in the group given.[27]

In another study conducted on the lung, it was shown that Dex reduces oxidative stress and prevents tissue damage by increasing superoxide dismutase (SOD) and glutathione (GSH) activities and decreasing myeloperoxidase (MPO) and malondialdehyde (MDA). However, it has been shown to stop inflammation by reducing TNF-α and IL-6, which induce inflammation.[28]

According to Arslan et al. Dex reduces the kidney injury by decreasing IL-6, TNF-a, and nuclear factor erythroid (NFR-2).[25] In another study, the effects of Dex on the liver were investigated and Bilgic et al. reported that Dex has healing properties by regulating oxidative stress (MDA, TOS, TAS, OSI, CAT, GSH, GSH Px, total nitrite), inflammation (IL 1β, IL 6, and TNF α), and apoptosis (caspase 3) in the liver.[29]

In our study, it was shown that Dex limits oxidative stress and inflammatory processes and minimizes kidney damage by preventing apatosis. At the same time, we could not find any study on its effect on ER-mediated apoptosis in our literature research. In addition, we have shown that TNF-a, and Cas 3 levels, which are different pathways of the ER-mediated apoptotic process, can be reduced, resulting in an improvement in the apoptosis process.

Conclusion

It has been shown in many studies that Dex has a protective effect against oxidative stress. However, its protective effect against real damage due to Dox has not been studied before. The results of our study showed that; Dex has shown that it can prevent the nephrotoxic side effects of Dox, as with other nephrotoxic agents. However, more studies are needed to clarify the protective effects and mechanisms of action of Dex.

Disclosures

Ethics Committee Approval: The experiment was carried out by the guidelines for the treatment and experimentation of animals provided in the pertinent European Communities Council Directive (86/609/EEC), and it was given the go-ahead by the Suleyman Demirel University Committee on Animal Research (Approval No.15.12.2022/08-110).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare no competing interests.

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Data Availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept – H.T.; Design – H.T., E.A.; Supervision – H.T., S.T.; Materials – M.A.S., M.E., S.T., E.A.; Data collection &/or processing – M.A.S., M.E., S.T.; Analysis and/or interpretation – H.T., M.A.S., E.A.; Literature search – M.A.S., M.E., S.T.; Writing – H.T.; Critical review – M.A.S., S.T., M.E.

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