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Research Article
Effect of Dexketoprofen Trometamol as Immunohistochemical and Electron Microscopy on Kidney in Rats

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Abstract

Background and Objective: Dexketoprofen trometamol is the dextrorotatory enantiomer of NSAID ketoprofen formulated as a tromethamine salt. This study aimed to perform immunohistochemical and electron microscopic evaluations of the effects of two different doses of dexketoprofen trometamol on kidneys via parenteral administration for 7 days. **Materials and Methods:** The study was conducted on 30 healthy, male Wistar albino rats, each weighing approximately 220 g. The rats were randomized and distributed across 3 groups, with 10 rats in each group. In the control group, 0.9% NaCl was used in 1 mL volume. In the other groups, and 16 mg kg^{-1}/day doses of dexketoprofen trometamol (Arveles 50 mg/2 mL) in 1 mL were used intraperitoneally twice per day for 7 days. **Results:** In the high-dose group, a statistically significant reduction in live weight was observed, along with apoptosis and increased cell proliferation when compared to the control group. In the low-dose group, statistically significant increased apoptosis and cell proliferation were found. **Conclusion:** It was found that dexketoprofen trometamol induced apoptosis and caused cell proliferation and the 16 mg kg^{-1}/day dose initiated the necrotic process. When an overdose of dexketoprofen trometamol (16 mg kg^{-1}) was administered, losses in live weight and diffuse degeneration of the kidney tissue occurred. Administrations of this dosage are not recommended as similar effects on human tissue are predicted.

Key words: Dexketoprofen trometamol, apoptosis, necrosis, rat, kidneys

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Competing Interest: The authors have declared that no competing interest exists.

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

INTRODUCTION

Pain is a global public health issue. Some studies have shown that if post-operative pain is not adequately managed it can result in chronic pain[1]. Non-steroidal anti-inflammatory drugs (NSAID) are the preferred agents for pain relief. They are non-addictive and have fewer side effects than other agents, which have been shown to cause constipation, respiratory depression and mental changes[2]. The NSAIDs may be used alone in the treatment of mild pain, but are often used in combination with opioids of varying strengths in the treatment of moderate pain. This heterogeneous group of non-analgesic drugs is used in the treatment of pain by bettering the analgesia or reducing the side effects brought on by analgesics[3]. The NSAIDs work by suppressing the synthesis of Prostaglandins (PG). The PG is the primary noxious mediator released from damaged tissue and this activation initiates the release of secondary and tertiary mediators. These can be a cause of hyperalgesia in traumatized tissue[4]. Some NSAIDs have key roles in processing nociceptive input in the dorsal horn[5]. The NSAIDs inhibit the synthesis of PGE_2 and PGI_2, which increase perfusion via vasodilation and stimulate sodium excretion and the secretion of renin in the kidneys. The effects of these lead to acute renal failure, hyperkalemia, sodium and water retention, nephrotic syndrome and interstitial nephritis. Dexketoprofen trometamol is the dextrorotatory enantiomer of NSAID ketoprofen formulated as a tromethamine salt. Various types of interactions and associated risks may occur with the use of NSAIDs and therefore, with dexketoprofen. Such interactions may involve the mechanism of action of dexketoprofen or the metabolic load[6]. It has been reported that dexketoprofen induces less intestinal toxicity than racemic ketoprofen and that this can be explained by the fact that it does not induce a remarkable change against oxidative stress[7].

Apoptosis is a cell death model that happens as a result of a gene-directed sequence of events. In addition to this, apoptosis can also occur as a result of pathological processes. The dysregulation of apoptotic signaling and inappropriate apoptosis are a factor in many diseases, autoimmune disorders and many types of cancer[8]. However, the reason for apoptosis induced by NSAIDs has not yet been entirely clarified[9].

Through the research of Ekici *et al.*[10] on intra-articular injected dexketoprofen trometamol (6.25 mg) on cartilage and synovium in rats and Hacibeyoglu *et al.*[11] on knee joints in rabbits injected with dexketoprofen trometamol (6.25 and 12.5 mg); it was determined that there is no significant histopathological damage on articular cartilage. Studies indicated that further electron microscopic studies are needed across a wider variety of animals in order to determine the effective and adverse doses of to be used in humans. The effects on kidney damage of both the recommended clinical dose level and of the high dose level have not yet been investigated. This study aimed to perform immunohistochemical and electron microscopic evaluation of the effects of dexketoprofen trometamol on kidneys in two different doses. The effects on kidney damage of recommended clinical dose level and increasing cumulative high dose level has not been previously investigated. The relationship found between dexketoprofen trometamol and apoptosis by immunohistochemical evaluation makes the study original.

MATERIAL AND METHODS

Experimental animals : Thirty healthy, male Wistar albino rats, weighing approximately 220 g each were used in the study. The study was conducted in the Animal Experiments Laboratory of Ankara University, after receiving approval from The Local Ethics Committee (No. 2009-44-200) for Animal Experiments of Ankara University. Prior to the study, the nutrition, living environments and night-day time conditions of the rats were standardized according to the optimal conditions.

For the experiment, the rats were randomized and distributed across 3 groups, with 10 rats in each group. In the control group, 0.9% NaCl was used in 1 mL volume. In the other groups, 8 and 16 mg kg^{-1}/day doses of dexketoprofen trometamol (Arveles 50 mg/2 mL) in 1 mL were used intraperitoneally twice per day for 7 days. The dexketoprofen trometamol (Arveles® 50 mg/2 mL ampule) used in the study was obtained from Ibrahim Ethem ULAGAY medicine, Istanbul, Turkey. The rats were euthanized with 80 mg kg^{-1} of Ketamine Hydrochloride (Ketalar, Pfizer) and their kidneys were removed.

Histological examination: The tissue samples were preserved in 10% formalin solution for the electron microscopic and immunohistochemical examination.

TUNEL assay: The TUNEL is a method that uses apoptotic processes and DNA fragmentation[12]. Apoptosis was expressed as a percentage of apoptotic cells in the total cells counted. The TUNEL index values for the two sections per rat were averaged to give the percentage of apoptosis in the renal tubules of each rat.

PCNA assay: Proliferation was determined by immunohistochemical staining with proliferating cell nuclear antigen (PCNA)[13]. After counterstaining and mounting, the PCNA-positive cells were counted in the tubules of two sections from each animal. It was expressed as a percentage of the total number of labeled cells divided by the total number of cells counted.

Statistical analysis: A one-way analysis of variance (ANOVA) procedure was used to test the hypothesis amongst the groups in order to make inferences about the population means. A Shapiro-Wilks test was performed to evaluate the assumption of normality for outcomes. Duncan's multiple comparison *post hoc* test was used to uncover the source of the significant difference among groups. Statistical analyses were conducted using Proc Glm in SAS 9.4. Results were presented as means and standard deviation and 95% confidence intervals were defined by an upper and lower limit which contains the population parameter of interest with probability p = 0.05.

RESULTS

The live weights and changes in live weights at the end of the experiment were given in the Table 1. At the end of the experiment, the highest live weight was found as 225.3±5.82 g in the control group, whereas, the lowest live weight was measured as 191.83±6.25 g in the high-dose group. At the end of the experiment, an increase of 2.10±1.85 g in weight was found in the control group, whereas weight losses of 6.20±1.21 and 32.33±6.24 g were measured in the low-dose group and high-dose group, respectively. With regards to change in live weights, no significant difference was found between the control and low-dose groups, whereas the change encountered in the high-dose group was found statistically significant.

Immunohistochemical results

Apoptotic results: The comparison between the groups when looking at apoptosis encountered using the TUNEL Method is given in Table 2. The TUNEL positive cells were identified in the distal and proximal tubules near the glomerulus in the control group. TUNEL-positive cells were also found sporadically in the collecting tubules (Fig. 1a, b). An increase in TUNEL-positive cells was noticeable in the tubules near the glomerulus in the low-dose group and the similarity of this in comparison to the control group was remarkable (Fig. 2a, b). In the high-dose group, TUNEL-positive cells were identified sporadically in the tubules near the glomerulus. In this group, TUNEL-positive cells in the collecting tubules were found in a lesser number than in the other groups (Fig. 3a, b).

PCNA results: Despite the fact that glomerular staining was observed sporadically in the kidney sections in the control group, the tubule cells encountered were remarkably PCNA positive. In the high magnification examination, most of the tubules where PCNA was observed were remarkably proximal tubules; the presence of positive cells in distal tubule cells was found to be much less. The PCNA, total PCNA and TUNEL data for the distal tubules of the kidneys and their significance levels are given in Table 1. The different doses of dexketoprofen trometamol that were administered had a statistically significant effect on the amount of distal tubular PCNA, total PCNA and TUNEL parameters of the kidney tissue.

In the control group, examinations of the medulla did not show any PCNA-positive cells at the cellular level, only insignificant stainings in the blood plasma (Fig. 4). In the kidney sections of the low-dose group, PCNA-uptake was found to be reduced throughout the tissue when compared with the control group. In the high magnification examinations, PCNA uptake was also detected in a small number of distal tubule cells and positive cells were also found in the parietal leaflet of the Bowman's capsule. In the low-dose group, examinations of the medulla showed no PCNA-positive cells at the cellular level, again, with the exception of insignificant staining observed in the blood plasma (Fig. 5). In the high-dose group, PCNA uptake was generally found to be in the distal tubule cells and additionally, immunoreactivity in the medulla was found to collect tubule cells differently than in the other groups (Fig. 6).

Table 1: Changes in live weights of the rats

Experimental groups	Initial live weights	Live weights at the end of experiment	Changes in live weights
Control group	223.20±6.59	225.30±5.82[a]	2.10±1.85[a]
Low-dose	227.40±6.37	221.20±5.88[a]	-6.20±1.21[a]
High-dose	224.17±4.79	191.83±6.25[b]	-32.33±6.24[b]
SED	3.95	3.72	1.74
Significance level	0.8777	0.0036	<0.001

[a,b]The differences between the mean values expressed by difference letters for the same characteristic in the same line are important (p<0.05). SED: Standard error of the difference between mean values

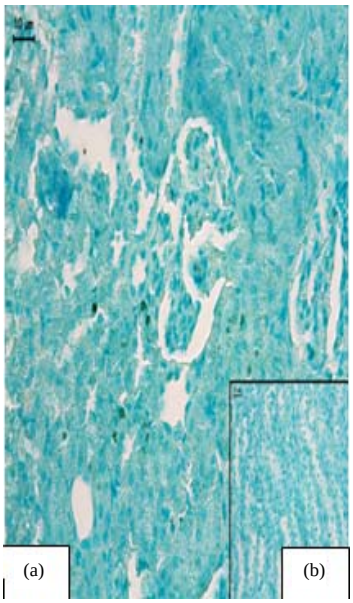


Fig. 1(a-b): Control group kidney tissue, (a) TUNEL X100 and (b) TUNEL X400

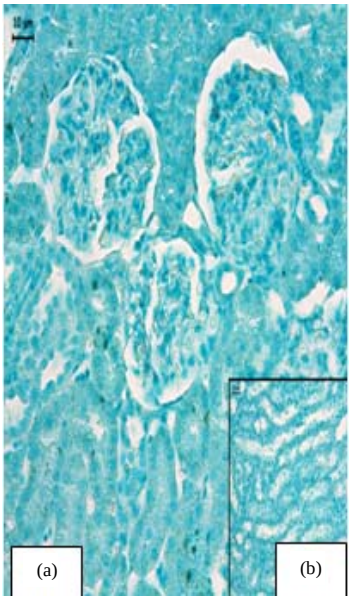


Fig. 2(a-b): Low-dose kidney tissue, (a) TUNEL X100 and (b) TUNEL X400

Table 2: Kidney distal tubule PCNA, total PCNA and TUNEL data sand their significance levels

Experimental groups	Distal tubule PCNA	Total PCNA	TUNEL
Control	19.250[a]	25.444[a]	0.722[b]
Low-dose	2.139[c]	1.806[c]	3.444[a]
High-dose	11.000[b]	17.917[b]	0.444[b]
SED	0.519	0.548	0.132
Significance level	0.001	0.001	0.001

Difference in group average shown with different letters in the same column is statistically important ($p<0.05$). SED: Standard error of the difference between mean values

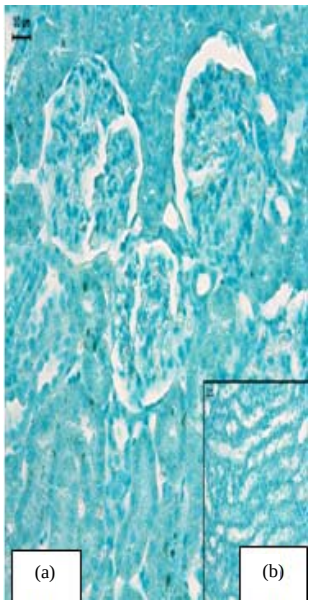


Fig. 3(a-b): High-dose kidney tissue, (a) TUNEL X100 and (b) TUNEL X400

It has been concluded, consequently, that the administration of the higher dose of the drug increased activation in the distal tubule and in the collecting ducts in the kidney sections and caused changes in the re-absorption mechanism of water and Na^+ ions.

Electron microscopic results: In the samples of the control group, it was observed via the electron microscope that the glomeruli were of a normal structure, as were the tubules, which had basement membranes, mitochondria, primary lysosomes and microvilli on their apical surface (Fig. 7). In the low-dose group, dilatation was somewhat apparent in the glomerular capillaries, while the general structure was found to be normal. In the examination of the tubules, relative thinness of the basement membrane compared with the control group was observed, as was the presence of numerous secondary lysosomes with miscellaneous dimensions in the cytoplasm. In this group, the secondary lysosomes were replaced by the primary lysosomes and autophagic vacuoles were seen. Additionally, vacuolar formations without a surrounding independent membrane were encountered. The mitochondria were seen to have a more active electron exchange compared to the control group and the mitochondria ion exchange exhibited more active features and impaired organization when compared to the control group and sporadic groups of the microvilli were noticeable (Fig. 8).

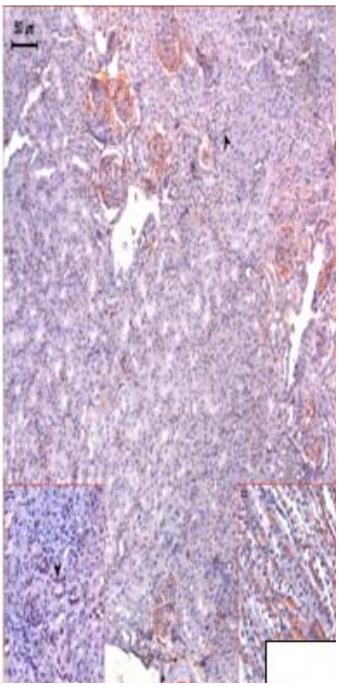


Fig. 4: Kidney section in the control group, PCNA: Positive proximal tubule cells
Big Figure: (Immunoperoxidase-hematoxyleneX100), Small figure: ImmunoperoxidaseX400

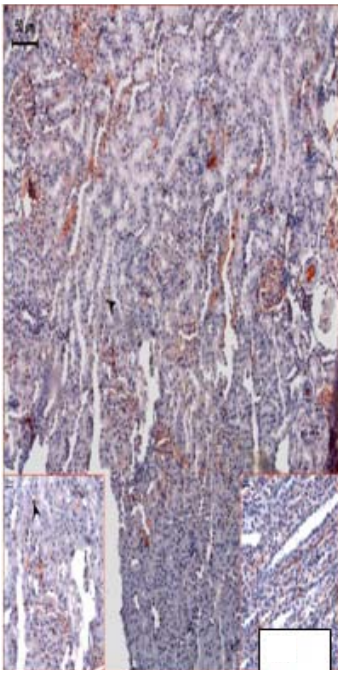


Fig. 5: Kidney section in the low-dose group, PCNA: Positive proximal tubule cells
Big Figure: (Immunoperoxidase-hematoxyleneX100), Small figure: ImmunoperoxidaseX400

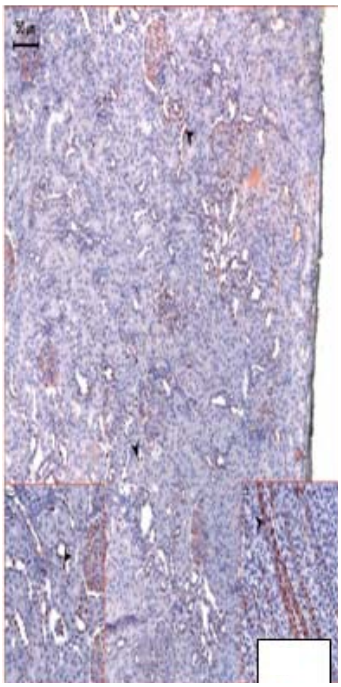
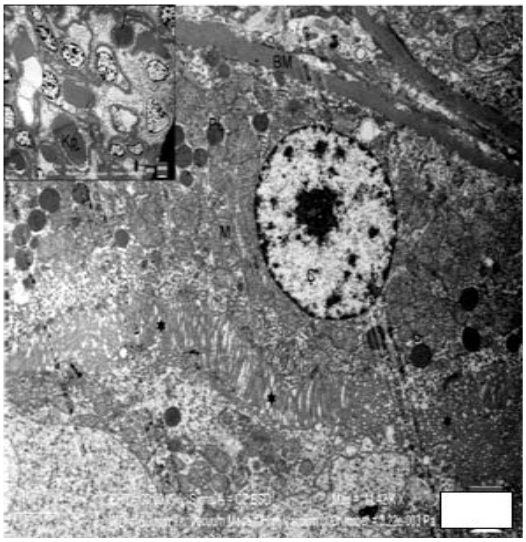


Fig. 6: Kidney section in the high-dose group, PCNA: Positive proximal tubule cells
Big Figure: (Immunoperoxidase-hematoxyleneX100), Small figure: ImmunoperoxidaseX400

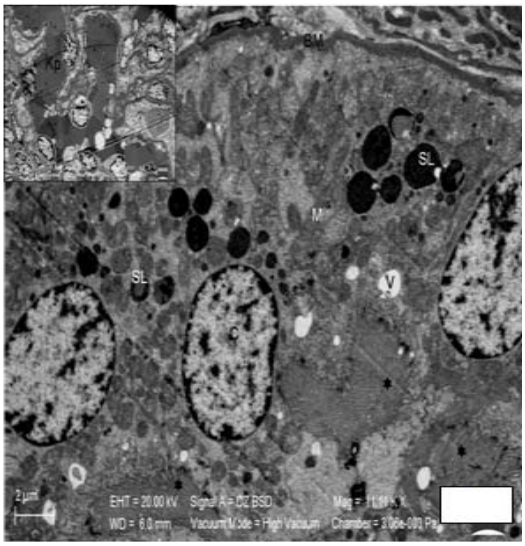
The electron microscopic examination of the glomeruli in the kidney sections of the high-dose group revealed noticeable hypertrophy in the podocytes. Another change observed in the glomeruli in this group was dense degeneration in the cells of the parietal leaflet of the Bowman's capsule. Examinations performed in the tubules demonstrated that the tubule cells were exposed to degenerative changes leading to death. The chromatin condensation in the nucleus, mitochondrial swelling and the disappearance of the mitochondria crista, secondary lysosomes filling the cell completely and lipid droplets developing due to impaired energy metabolism were remarkable. The microvilli had a 'hairy' appearance and a normal organizational structure was not observed. In this group, the basement membrane was seen to be thinner than in the control group; however, it had thickened remarkably in the regions with dense cell degeneration (Fig. 9).

The immunohistochemical and electron microscopic findings in this study revealed that the high-dosage of dexketoprofen trometamol in particular caused injury to the collecting tubules in the kidney tissue and negatively affects the reabsorption of water and Na^+ ions. The glomeruli of the control group were observed to be normal in the samples, while in those of the low-dose group a relative dilatation was



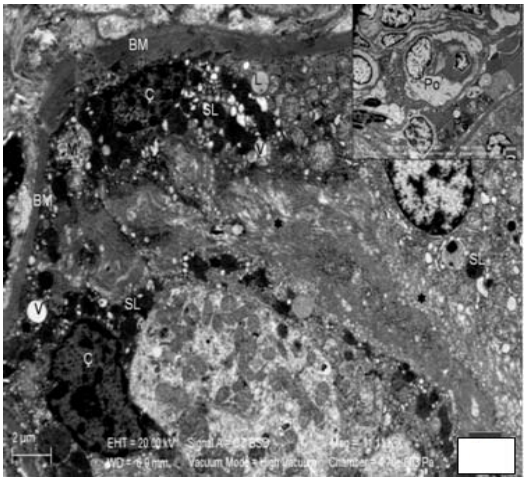
	Microvilli
C:	Nucleus of the tubule cells
PL:	Primary lysosomes
M:	Mitochodondrium
BM:	Basement membrane
Small are:	Glomerulus
Cp:	Caapillary (uranylacetate-leadcitrate)

Fig. 7: Control group; electron microscopic examination of kidney



	Microvilli forming irregular group
C:	Nucleus of the tubule cells
SL:	Secondary lysosomes
V:	Vacuole
M:	Mitochondrium
BM:	Basement membrane
Small are:	Glomerulus
Cp:	Dilatedcapillary (uranylacetate-leadcitrate)

Fig. 8: Low-dose group, electron microscopic examination of kidney



	Microvilli as the irrefular fiber
C:	Nucleus of the tubule cells
SL:	Secondary lysosomes
V:	Vacuole
PL:	Primary lysosomes
M:	Swollen mitochondrium
BM:	Thinned and sporadically thickened basement membrane
Small are:	Glomerulus
Po:	Hypertrophicpodocye
Pa:	degenerated parietal epithelial cell (uranylacetate-leadcitrate)

Fig. 9: High-dose group, electron microscopic examination of kidney

noticed in the glomerular capillaries, however, the general structure was evaluated as normal. Thinning in the basement membrane of the tubules when compared to the control group was noticed, as was the presence of numerous secondary lysosomes with various dimensions within the cytoplasm. The glomeruli, tubular basement membrane, mitochondria, primary lysosomes and microvilli at the apical surface were all seen to be of normal structure. In the high-dose group, hypertrophic podocytes, dense degeneration in the parietal leaflet cells of the Bowman's capsule, dense degenerative changes in the tubule cells, a 'hairy' appearance in the microvilli and abnormal organizational development were all observed.

In the immunohistochemical evaluation of the apoptotic cells in the kidney cells, the low-dose of dexketoprofen trometamol was found to increase apoptosis in the glomerulus, whereas high-dose dexketoprofen decreased apoptosis. Conversely, in the evaluation of the cell proliferation, a low-dose of dexketoprofen trometamol was shown to decrease cell proliferation in the glomerulus and the high-dose of dexketoprofen was shown to increase it.

Electron microscopic examinations revealed that dexketoprofen trometamol caused degeneration in the parenchymal cells in particular. Also, significant weight loss

was observed in the rats who were administered with the high-dose of dexketoprofen trometamol during the study. Consequently, it has been concluded that, depending on the dosage of the drug, drug administration increased activation in the parenchymal cells in particular, which then resulted in cell degeneration and this degeneration was then seen to have a remarkable effect upon the kidneys.

DISCUSSION

Renal side effects are observed in 18% of patients who receive treatment with NSAIDs and the incidence of serious renal side effects is 1% in the subjects who showed clinical symptoms[14]. The NSAID use was associated with 3% of all acute renal failure cases and it was also found to be the cause of illness in 30% of patients with end-stage renal failure[15]. NSAIDs have lower renal hemodynamic effects than sulindac and salsalate. Sulindac and salsalate instigate these effects by increasing renal prostaglandin synthesis and decreasing prostaglandin inhibitors respectively[16]. Conversely, researchers have reported that NSAID-induced nephropathy develops due to sulindac. As a consequence, there is a risk of the development of NSAID-induced nephropathy[17]. Kuo *et al*.[18] have reported that clinical progression from minimal influence at the cellular level to terminal-stage renal injury induced by aspirin or other NSAIDs, occurs depending on dosage. Kon *et al*.[19] and Oh *et al*.[20] have shown through similar studies at different times, that salicylate decreases the threshold for an increase in the mitochondrial permeability of the kidney and liver of the rat. This condition induces apoptosis and leads to the development of dysfunction and to necrosis in the advanced stages.

The development of weight loss during the study in the rats who received the high-dose of dexketoprofen trometamol is compatible with the data from other studies which showed that NSAIDs caused a decline food intake in the *ad libitum* fed rats by reducing appetite, which consequently, led to decreases in their live weights[21]. The reduction in live weights in both groups administered with the drug is considered to be associated with both appetite loss due to the drug and also with the impaired integrity of gastrointestinal mucosa caused by dexketoprofen trometamol inhibiting the COX-1 synthesis.

Apoptosis, a cell death model that is genetically regulated, is an event that leads to the deformation of cell membranes, cell leakage the condensation of nuclear chromatin and the activation of endonucleases. Apoptosis is an active process regulated by the cell nucleus and may be triggered by proinflammatory cytokines, genetic factors, ultraviolet rays and radiation, thermal shock, hypoxia, an absence of growth hormone and growth factor, DNA-damaging agents, anti-cancer drugs, oxygen radicals, intracellular acidification and other metabolic drugs[22]. Apoptotic cells are cleaned by the local phagocytes. It is accepted that the active suppression of apoptosis plays a role in the pathophysiology of cancer and autoimmune diseases, while increased apoptosis leads to the occurrence of ischemic injury and acquired immune deficiency syndrome. It has been suggested that altered gene expression may play a role in the development of sepsis and shock. Bock *et al*.[23] have tested the relative anti-proliferative activities of NSAIDs and reported that ketoprofen has a moderate-degree of anti-proliferative activity and causes a high level of apoptosis. Zimmermann *et al*.[24] have investigated the apoptotic effect of aspirin in their study and demonstrated that it induces apoptosis, shown by it causing the increase in the release of Cytochrome C from mitochondria.

This study evaluated cell apoptosis through the TUNEL Method and detected a significantly increased level of apoptosis in the tubules near the glomerulus in the group administered the high-dose of dexketoprofen trometamol compared to the control group. A similar rate of apoptosis to the control group, however, was found in the collecting tubules. Reduced levels of apoptosis in the collecting tubules were found when compared to the other groups, however.

Inal *et al*.[25] compared the effects of dexketoprofen trometamol, meloxicam and diclofenac sodium on kidney and liver tissues in the treatment of fibula fracture in their experimental study. Through the histopathological analysis of kidney and liver tissue, they observed that meloxicam and diclofenac have no effect on glomerular injury or fibrosis interstitial inflammation. It was found that the dexketoprofen trometamol group was high-grade fibrotic in the kidney when compared with the control group and had no effect on glomerular injury or interstitial inflammation. This finding was compatible with the observations in present study of the histopathological effect of low-dose dexketoprofen trometamol on kidneys. In that study, it was generally found that degrees of tubular necrosis and tubular vacuolization were significantly higher when compared with the control group, however, no significant difference was detected between the dexketoprofen trometamol, meloxicam and diclofenac groups.

CONCLUSION

It can be concluded that no significant change in cellular structure was encountered in the low-dose group compared to the control group, however, an increase in apoptosis was noticed. A significant decrease in apoptosis and diffuse degenerative changes throughout tissue were observed in the high-dose group compared to the low dose group. According to the results of this study, it can be said that the decrease in levels of apoptosis in high doses of the drug can be considered as a decrease in cellular defense. This first and original study involving electron microscopic examination and immunohistochemical evaluation of the effect of dexketoprofen trometamol on kidney injury should be supported by further studies.

When dexketoprofen trometamol is administered in high levels (16 mg kg^{-1}), losses in weight cause diffuse degeneration in the kidney tissue. Thus, administration of the drug in larger amounts is not recommended since a similar effect on human tissue is predicted.

SIGNIFICANCE STATEMENT

This study discovers the relationship between dexketoprofen trometamol and apoptosis by evaluating the immunohistochemical tests. The electron microscopic examination was done for the very first time on dexketoprofen trometamol which makes original study. Further studies are needed on vast range of animals in order to check its severe effects on humans.

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