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Effect of tenoxicam on rat liver tissue

Tenoksikamın sıçan karaciğeri üzerine etkisi

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Background/aims: *Tenoxicam is a non-steroidal antiinflammatory drug, which has antipyretic and antiinflammatory effects. Though it is known that the major side effect of non-steroidal antiinflammatory drugs is on the gastrointestinal tract and liver, there have been few studies regarding the effects of tenoxicam. In this study, we aimed to investigate whether tenoxicam has a deleterious effect on liver tissue using immunohistochemical staining and biochemical analysis.* ***Methods:*** *A total of 30 male Wistar albino rats were included in this study. Animals were equally and randomly divided into three groups as follows: Group I (Controls), Group II (Injection with 10 mg/kg/day of tenoxicam) and Group III (Injection with 20 mg/kg/day of tenoxicam). At the end of the study, some liver tissue samples were taken and kept in neutral formalin for histological and immunohistochemical evaluation. Liver tissue samples were embedded in paraffin blocks after routine tissue preparation procedures, and were stained with hematoxylin-eosin and immunohistochemical stain. Liver samples taken for biochemical analysis were washed with physiological saline. Thiobarbituric acid reactive substances and superoxide dismutase activity were measured in the obtained supernatants.* ***Results:*** *There were significant structural changes in liver tissues of the tenoxicam-administered groups when compared with the controls. We observed that hepatic (inducible nitric oxide synthase) receptors were increased in the study groups. Furthermore, hepatic superoxide dismutase and malondialdehyde levels were prominently higher in the tenoxicam-administered groups when compared to levels of the control group.* ***Conclusions:*** *Nitric oxide may exert an antioxidative effect against lipid peroxidation to one point at low levels; however, it may also have the opposite effect at higher levels in tenoxicam induced liver injury.*

Key words: Tenoxicam, inducible nitric oxide synthase, hepatotoxicity, superoxide dismutase, malondialdehyde

Amaç: *Tenoksikam antipiretik ve antiinflamatuvar özelliklere sahip non-steroidal antiinflamatuvar ilaçlar grubundandır. Bilindiği gibi non-steroidal antiinflamatuvar ilaçlarlar en çok yan etkisini gastrointestinal sistem ve karaciğer üzerinde göstermektedir. Bu çalışmada tenoksikamın karaciğer üzerinde olan zararlı etkilerini immunohistokimyasal ve biyokimyasal yöntemler kullanarak belirlemeyi amaçladık.* ***Yöntem:*** *Bu çalışmada toplam 30 adet Wistar albino cinsi erkek sıçan kullanıldı. Hayvanlar eşit olarak ve rastgele üç gruba ayrıldı ve gruplar şu şekilde oluştu: Grup I (Kontrol), Grup II 10 mg/kg/gün IM tenoksikam verilen grup ve grup III 20 mg/kg IM tenoksikam verilen grup. Çalışma sonunda hayvanlar kesilerek karaciğer doku örneklerinin bir kısmı histopatolojik inceleme için %10 nötral formalinde tespit edildi ve rutin takip yöntemlerinden sonra hematoksilen-eozinle boyanarak incelendi. Biyokimyasal inceleme için alınan karaciğer örnekleri fizyolojik su ile yıkandı. Süpernatantları elde edilerek tiobarbiturik asit reaktiv madde ve süperoksid dismutaz aktivitelerine bakıldı.* ***Bulgular:*** *Tenoksikam verilen gruplar ile kontrol grubu arasında belirgin yapısal değişiklikler görüldü. Deney gruplarında hepatik indüklenebilir nitrik oksit sentaz reseptör artışı gözlendi. Ayrıca hepatik superoksid dismutaz süperoksid dismutaz ve malondialdehid seviyelerinde de kontrol grubu ile kıyaslandığında yüksek değerler bulundu.* ***Sonuç:*** *Tenoksikama bağlı karaciğer hasarında, nitrik oksit belirli oranlarda lipid peroksidasyonu engelleme yönünde etkin ancak yüksek dozlarda ise aksi yönde etki göstermektedir.*

Anahtar kelimeler: Tenoksikam, indüklenebilir nitrik oksit sentaz, karaciğer hasarlanması, superoksid dismutaz, malondialdehit

INTRODUCTION

Analgesics are separated into two different groups as narcotic and non-narcotic analgesics. Among non-narcotic analgesics, non-steroidal antiinflammatory drugs (NSAIDs) are widely used. Tenoxicam is a NSAID of the oxicam family, which has antipyretic and anti-inflammatory effects. It strongly inhibits the cyclooxygenase enzyme (1, 2). The elimination of this drug is mainly in the liver, and this process does not depend on age, gender or hepatic/renal failure conditions. Tenoxicam has the longest elimination half-life among NSAIDs (3–5). Several NSAIDs have been associated with liver damage.

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The frequency of NSAIDs-related hepatic injuries has differed in the French and Spanish databases (6). Friis et al. (7) reported that the incidence of hepatic injury due to sulindac was estimated to be 18-fold higher than that due to ibuprofen. Although it is well known that the side effects of NSAIDs are prominently on the gastrointestinal system and liver, there are few studies regarding the effects of tenoxicam. Different researchers reported that tenoxicam causes acute hepatitis (8, 9). Thus, it is not clear whether tenoxicam leads to a structural change in liver tissue.

On the other hand, nitric oxide (NO) is a compound with high oxidation capacity, which is produced from L-arginine amino acid via inducible NO synthase (iNOS) enzyme in hepatocytes and other connective tissue cells in the liver (10–17). Therefore, it can be suggested that there is a positive correlation between liver damage and increase in NO levels. For this reason, lipid peroxidation and iNOS enzyme expression are considered as robust markers in determining the structural damage in hepatic tissue (18–21). In this study, we aimed to investigate whether tenoxicam has a deleterious effect on liver tissue using immunohistochemical staining and biochemical analysis methods.

MATERIALS AND METHODS

Animals

A total of 30 male Wistar albino rats weighing 200±20 g were included in this study. Animals were kept in individual plastic cages with bedding under standard laboratory conditions and were given rat food and tap water ad libitum. All animals were maintained and used in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals prepared by Süleyman Demirel University.

Experimental Design

Rats were randomly and equally divided into three groups as follows: Group I (Controls, only saline injection), Group II (Injection with 10 mg/kg/day of intramuscular tenoxicam for 10 days) and Group III (Injection with 20 mg/kg/day of intramuscular tenoxicam for 10 days). While we did not find any related literature for the dose used in Group II, we referred to a study of a fracture model for dose determination (22).

At the end of the study, rats were sacrificed under ketamine/xylazine anesthesia. Blood and liver tissue samples were collected from all animals. Some parts of the liver tissues were taken into phosphate buffered saline (PBS) solution for biochemical analysis, whereas the remaining parts were kept in neutral formalin for histological and immunohistochemical evaluation. Liver tissue samples were embedded in paraffin blocks after routine tissue preparation procedures, cut at 5 micrometers with a microtome blade and stained with hematoxylin-eosin and immunohistochemical stain. Slides were examined under Olympus BX-50 light microscope. Tissues were evaluated according to the semi-quantitative scoring method.

Biochemical Analysis

For biochemical analyses, tissue samples of the left livers were washed with physiological saline. They were then homogenized for 5 minutes (min) in a homogenizer (Ultra-Turrax T25, Germany) with 50 mM cold phosphate buffer pH=7.4 in order to collect 10% homogenate. These homogenates were centrifuged at 6000 g for 10 min to obtain supernatants. Thiobarbituric acid reactive substances (TBARS) and the activities of superoxide dismutase (SOD) were determined in the supernatants (23).

Superoxide dismutase was measured according to the principle in which xanthine reacts with xanthine oxidase to generate super oxide radicals, which react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT) to form a red formazan dye. The SOD activity was then measured by the degree of inhibition of this reaction (24).

Thiobarbituric acid reactive substances were determined by double heating method of Draper and Hadley (25). The principle was based on the spectrophotometric measurement of the color occurring during the reaction to TBA with malondialdehyde (MDA). For this purpose, 2.5 ml of 100 g/L trichloroacetic acid (TCA) solution was added to 0.5 ml homogenate in a centrifuge tube and placed in a boiling water bath for 15 min. After cooling under tap water, the mixture was centrifuged at 1000 g for 10 min, and 2 ml of the supernatant was added to 1 ml of 6.7 g/L TBA solution in a test tube and placed in a boiling water bath for 15 min. The solution was then cooled under the tap water and its absorbance was measured at 532 nm. Concentration of TBARS was calculated by the absorbance coefficient of the MDA-TBA complex 1.56 x 105 cm^{-1} M^{-1} and expressed in nmol/g protein.

An autoanalyzer, Olympus AU640 (Japan), was

used to determine the activities of SOD and glutathione peroxidase (GSH-Px), and a spectrophotometer, Shimadzu UV-1202V (Japan), was used to estimate the other parameters.

Histological Evaluation

Stained slides were read by a scientist blinded to the study groups and graded according to a modified scoring system developed by Abdel-Wahhab et al. (26). Liver specimens were stained with hematoxylin and eosin and evaluated by four observers. Liver injury was graded from (-), no damage, to (+++), severe damage, in nine categories: granular degeneration of hepatocytes, vascular congestion, perivascular mononuclear cell infiltrations, cell group necrosis, pyknotic nucleus, mononuclear cell infiltrations in parenchyma, mononuclear cell infiltrations in portal tracks, hemorrhage, and the proliferations of bile ducts.

Immunohistochemical Evaluation

Liver specimens were obtained and placed in 10% neutral buffered formalin for 24 hour (h). Liver sections were cut at 4 microns and placed on special lysine lams and were kept at room temperature overnight for desiccation. Primary iNOS antibody (epitope-specific rabbit antibody, Labvision Fremont, CA, USA), diluted 1: 50 in PBS, was added and incubated for 1 h at room temperature and washed with PBS. Slides were read by four scientists blinded to the study groups and graded from one negative (-) to three positives (+++). Slides were evaluated as described previously (22, 27).

Statistical Analysis

SPSS 15.0 software was used for statistical analysis. All results were expressed as means ± SD. To determine the effect of treatment, data were analyzed using chi-square, Kruskal-Wallis and Mann-Whitney U tests. P values less than 0.05 were considered significant.

RESULTS

Biochemical Results

Mean SOD and MDA values of the groups are given in Table 1.

Table 1. Mean SOD and MDA values according to groups

Groups	MDA	SOD
Control (I)	311.1 ± 66.7	418.4 ± 49.9
10 mg/kg group (II)	386.3 ± 91.9	506.4 ± 41.7
20 mg/kg group (III)	524 ± 63.4	541 ± 57.6

Hepatic SOD levels of the control group were significantly lower when compared with the tenoxicam-administered groups ($p<0.05$), but there was no significant difference between Groups II and II-I ($p>0.05$) (Figure 1).

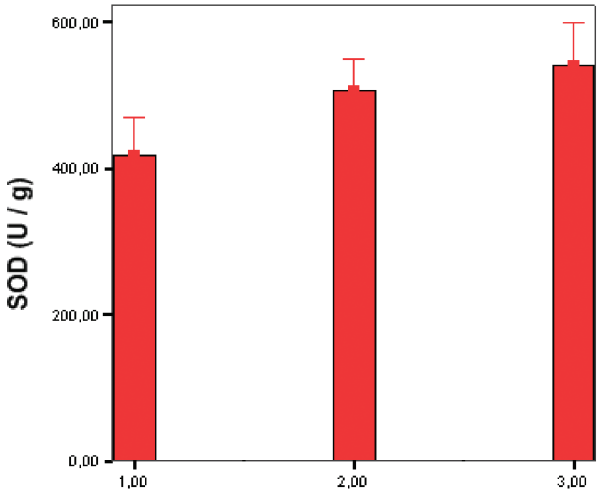

Figure 1. SOD enzyme activity levels in liver tissue samples of Groups I and II. The difference between Groups I and III was statistically significant ($p<0.005$), but there was no significant difference between Groups II and III ($p>0.005$).

Hepatic MDA levels of the control group were significantly lower when compared with the tenoxicam-administered groups ($p<0.05$), but there was no significant difference between Groups II and II-I ($p>0.05$) (Figure 2).

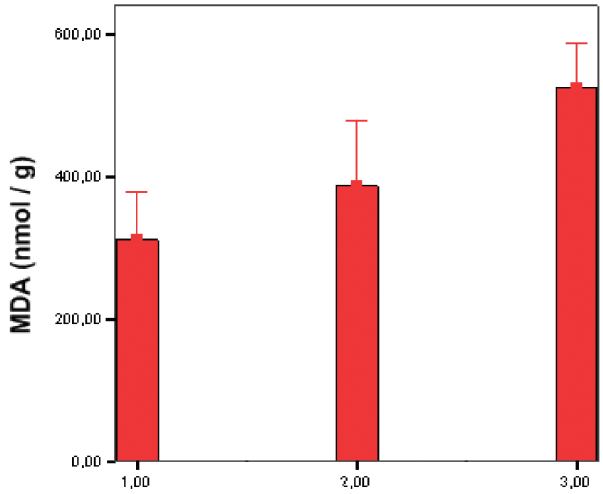

Figure 2. The levels of MDA (TBARS=MDA) in liver tissues. The difference between The difference between Groups I and III was statistically significant ($p<0.005$), but there was no significant difference between Groups II and III ($p>0.005$).

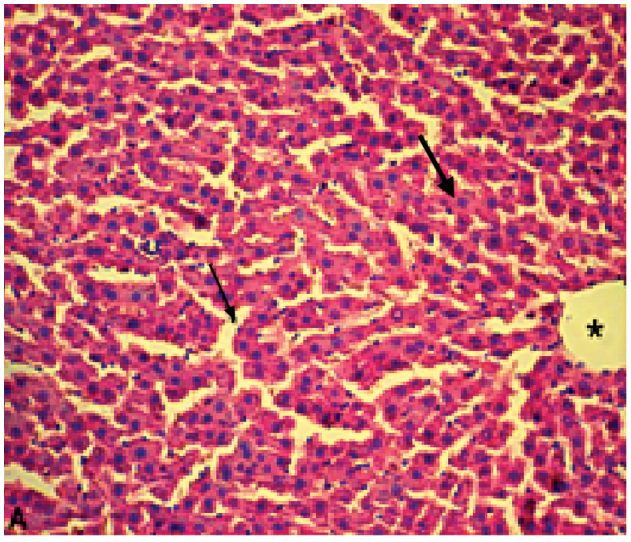

Figure 3. Group I (saline solution): Hepatocytes (thick arrow), sinusoids (thin arrow) and central vein (asterix) in normal apperance (Hematoxylin-Eosin) (A: x240)

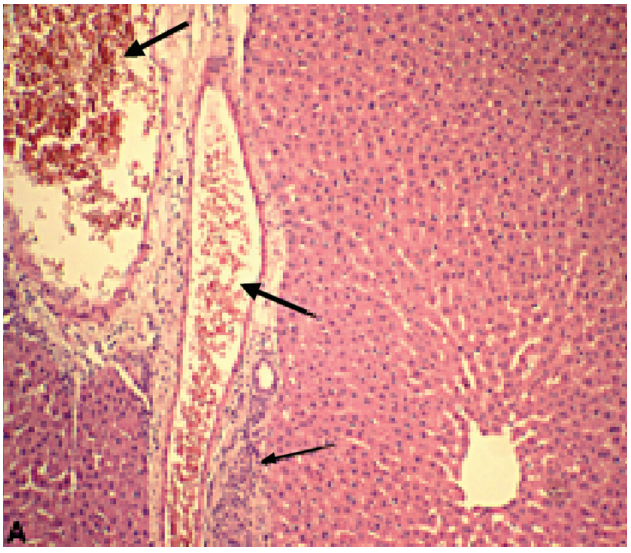

Figure 5. Group III (20 mg/kg tenoxicam): Vascular congestion (thick arrow), mononuclear cell infiltration (thin arrow) (Hematoxylin-Eosin) (A: x120).

Histopathological Results

In histopathological evaluation of the liver tissue samples, there was no significant change in Group I (Figure 3). In Group II, there were granular degenerations in hepatocytes, necrotic cell groups, cells with pyknotic nuclei, and mononuclear cell infiltrations in perivascular and portal triad areas, and these changes were statistically significant when compared with the controls ($p<0.05$) (Figure 4). In liver tissue samples of Group III, it was observed that there were structural changes similar to those of Group II, except that there was a greater increment in mononuclear cell infiltration, bile duct proliferation and necrotic cell amount, and this increase was statistically significant when compared with Group II ($p<0.05$) (Figure 5).

Immunohistochemical Results

We observed very slight staining in perivascular and parenchymal regions of the liver tissue samples of Group I, scored as one negative / positive (- / +) (Figure 6). Staining degree was scored as (+) in Group II (Figure 7) and (++) in Group III in the same areas (Figure 8). There was a statistically significant difference between the controls and study

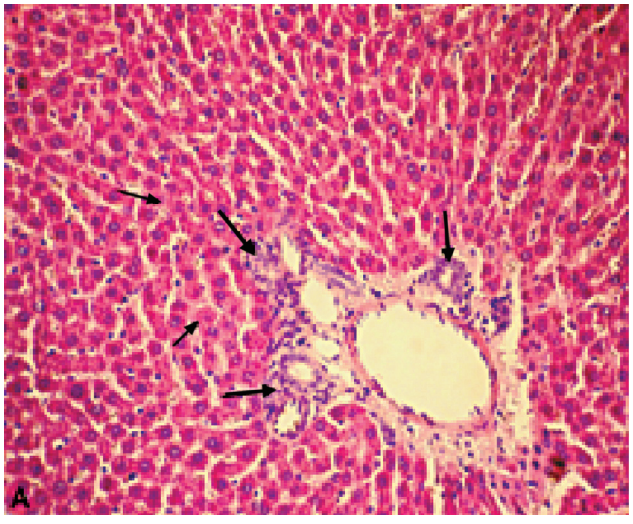

Figure 4. Group II (10 mg/kg tenoxicam): Picnotic nucleus in hepatocytes (thin arrow), proliferation on bile duct (thin arrow) (Hematoxylin-Eosin) (A: x240)

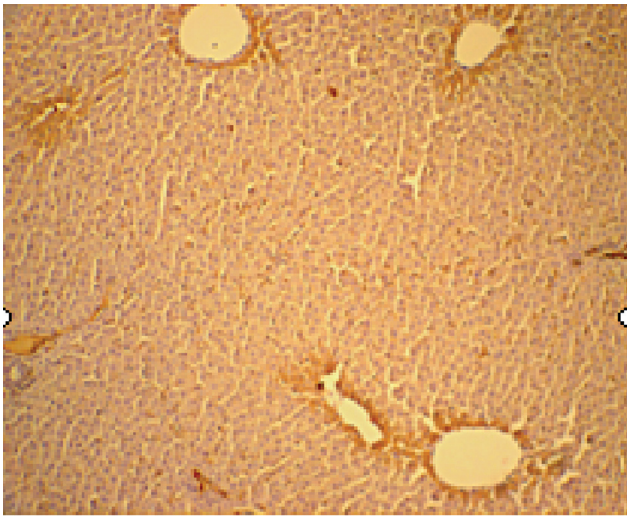

Figure 6. Control group liver tissues cental vein, mainly painted one positive areas are selected (İNOS immun staining, x240)

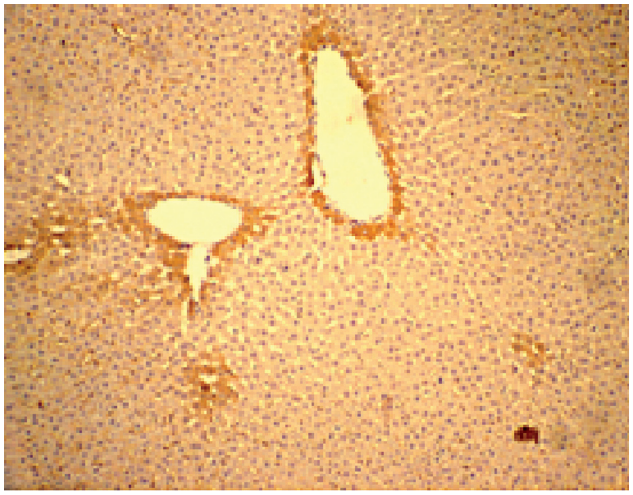

Figure 7. 10 mg/kg tenoxicam group Tissues cental vein, mainly painted two positive areas are selected (İNOS immun staining, x240)

groups ($p<0.05$). There was a positive correlation between the staining grade and administered tenoxicam dose.

DISCUSSION

Several researchers reported that tenoxicam may lead to liver damage. However, this condition definitely has not been shown. In this study, we aimed to investigate whether tenoxicam has such a dose-dependent effect on the liver tissue. We observed some dose-dependent structural changes like granular degeneration in hepatocytes, pyknotic nucleus, proliferation in bile duct, sinusoidal dilatation, vascular congestion, and mononuclear cell infiltrations in perivascular and portal areas. These findings are hepatitis. Our findings are supported by different researchers (8,9). It is not possible to determine the mechanism of injury with histopathology; immunohistochemical staining results are necessary. In our study, we observed that liver tissues of the control group were only slightly stained with immunohistochemical staining, whereas there was a graded dose-dependent increase in staining of the liver tissues from the study groups (27).

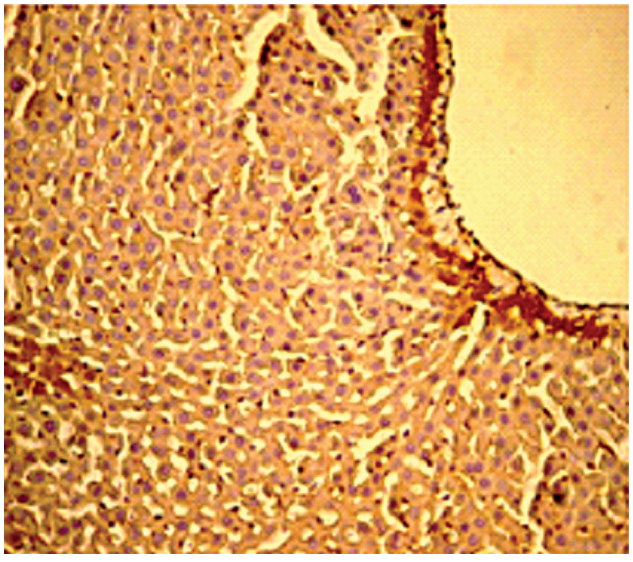

Figure 8. 20 mg/kg tenoxicam group mainly painted three positive areas are selected (İNOS immun staining, (İNOS immun Staining, x400)

In other previous studies regarding liver ischemia / reperfusion and cirrhosis models, it has been reported that the intensity of iNOS enzyme receptor expression was increased (28, 29). Zhu et al. (30) found that there was an increase in iNOS expression levels in CCl4-induced acute liver damage and NO has a decreased lipid peroxidation level. Doğru-Abbasoğlu et al. (31) suggested that MDA-induced tissue damage was ameliorated via inhibition of iNOS expression. It has been indicated that iNOS was expressed in hepatocytes and inflammatory cells during the early stages of cirrhosis (27, 32).

Inducible nitric oxide synthase (iNOS) expression was also shown to be present in healthy individuals; however, the amount of expression increases under certain conditions such as cirrhosis (33, 34). The high levels of hepatic NO are related with hepatotoxicity (35). It has been reported that iNOS expression levels were higher in ethanol-induced chronic liver damage, suggesting a marker role for iNOS in destructive conditions (36). In this case, NO is normally produced in liver tissue, but it increases under pathological conditions (37, 38). In our view, this increase shows the hepatotoxicity. Hepatotoxicity is linked to lipid peroxidation. Several researchers reported that NO enhanced the lipid peroxidation levels (39-41). Lipid peroxidation damage in the cell creates while such as SOD and MDA antioxidant systems is engaged. MDA and SOD attempt to prevent lipid peroxidation. It is known that the MDA level does not change or slightly increases and that SOD levels increase in the acute phase. Özgöçmen et al. (42) reported that there was no statistically significant change in MDA levels of the group given tenoxicam for four weeks when compared with the controls. In another study, it was found that tenoxicam, which was intraperitoneally administered to patients with peritonitis at a dose of 0.5 mg/kg, had no ef-

fect on MDA levels (43). In our study, we found that increment in SOD levels has an antioxidant effect; however, it was not enough to interfere with lipid peroxidation. That may be because we used higher doses of tenoxicam compared to those of the previous studies.

In conclusion, we have identified that tenoxicam is hepatotoxic, especially at a dose of 20 mg/kg. Dose-dependent increase in the intensity of immune staining may indicate an increase in NO levels in parallel to iNOS receptor distribution. We have concluded that NO may exert an antioxidative effect against lipid peroxidation to one point at low levels; however, it has the opposite effect at higher levels, and this evidence is also in accordance with the previous studies.

REFERENCES

1. Binder D, Hromatka O, Geissler F, et al. Analogues and derivatives of tenoxicam. Synthesis and antiinflammatory activity of analogues with different residues on the ring nitrogen and the amide nitrogen. J Med Chem 1987; 30: 678–82.
2. Kayaalp O. Tıbbi Farmakoloji. 10. baskı. Ankara: Hacettepe-Taş Kitapçılık, 2002; 960–86.
3. Burdan F, Szumilo J, Klepacz R, et al. Gastrointestinal and hepatic toxicity of selective and non-selective cyclooxygenase-2 inhibitors in pregnant and non-pregnant rats. Pharmacol Res 2004; 50: 533-43.
4. Guentert TW, Heintz RC, Joly R. Overview on the pharmacokinetics of tenoxicam. Eur J Rheumatol Inflamm 1987; 9: 15–25.
5. Nilsen OG. Clinical pharmacokinetics of tenoxicam. Clin Pharmacokinet 1994; 26: 16–43.
6. Lapeyre-Mestre M, Bareille MP, Del Pozo JG, et al. Nonsteroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. Fundam Clin Pharmacol 2006; 20: 391-5.
7. Friis H, Andreasen PB. Drug-induced hepatic injury: an analysis of 1100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. J Intern Med 1992; 232: 133-8.
8. Sungur C, Ates B, Akbas O. Acute hepatitis caused by tenoxicam. Ann Pharmacother 1994; 28: 1309.
9. Katsinelos P, Katsos I, Patsiaoura K, et al. Tenoxicam-associated hepatic injury: a case report and review. Eur J Gastroenterol Hepatol 1997; 9: 403-6.
10. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med 1993; 329: 2002–12.
11. Laskin DL, Rodriguez del Valle M, Heck DE, et al. Hepatic nitric oxide production following acute endotoxemia in rats is mediated by increased nitric oxide synthase gene expression. Hepatology 1995; 22: 223-34.
12. Laskin DL, Heck DE, Gardner CR, et al. Distinct patterns of nitric oxide production in hepatic macrophages and endothelial cells following acute exposure of rats to endotoxin. J Leukoc Biol 1994; 56: 751-8.
13. Feder LS, Laskin DL. Regulation of hepatic endothelial cell and macrophage proliferation and nitric oxide production by GM-CSF, M-CSF and IL-1 beta following acute endotoxemia. J Leukoc Biol 1994; 55: 507-13.
14. Helyar L, Bundschuh DS, Laskin JD, et al. Induction of hepatic Ito cell nitric oxide production after acute endotoxemia. Hepatology 1994; 20: 1509-15.
15. Nussler AK, Geller DA, Sweetland MA, et al. Induction of nitric oxide synthesis and its reactions in cultured human and rat hepatocytes stimulated with cytokines plus LPS. Biochem Biophys Res Commun 1993; 194: 826-35.
16. Curran RD, Billiar TR, Stuehr DJ, et al. Hepatocytes produce nitrogen oxides from L-arginine in response to inflammatory products of Kupffer cells. J Exp Med 1989; 170: 1769-74.
17. Gardner CR, Heck DE, Feder LS, et al. Differential regulation of reactive oxygen and nitrogen intermediate production by hepatic macrophages and endothelial cells. In: Jesaitus A, Dratz E, eds. The molecular basis of oxidative damage by leukocytes. Boca Raton, FL: CRC Press, 1992; 267-72.
18. Thiemermann C, Ruetten H, Wu C-C, et al. The multiple organ dysfunction syndrome caused by endotoxin in the rat: attenuation of liver dysfunction by inhibitors of nitric oxide synthase. Br J Pharmacol 1995; 116: 2845-51.
19. Decker KF, Obolenskaya MY. Cytokines, nitric oxide synthesis and liver regeneration. Gastroenterol Hepatol 1995; 10: 12-7.
20. Gross SS, Wolin MS. Nitric oxide: pathophysiological mechanisms. Annu Rev Physiol 1995; 57: 737-69.
21. Chamulitrat W, Blazka ME, Jordan SJ, et al. Tumor necrosis factor-a and nitric oxide production in endotoxin-primed rats administered carbon tetrachloride. Life Sci 1995; 24: 2273-80.
22. Giordano V, Giordano M, Knackfuss IG, et al. Effect of tenoxicam on fracture healing in rat tibiae. Injury 2003; 34: 85–94.
23. Magwere T, Naik YS, Hasler JA. Effects of chloroquine treatment on antioxidant enzymes in rat liver and kidney. Free Radic Biol Med 1997; 22: 321-7.
24. Woolliams JA, Wiener G, Anderson PH, McMurray CH. Variation in the activities of glutathione peroxidase and superoxide dismutase and in the concentration of copper in the blood in various breed crosses of sheep. Res Vet Sci 1983; 34: 253-6.
25. Draper HH, Hadley M. Malondialdehyde determination as index of lipid peroxidation. Methods Enzymol 1990; 186: 421-31.
26. Abdel-Wahhab A, Nada SA, Arbid MS. Ochratoxicosis: prevention of developmental toxicity by L-methionine in rats. J Appl Toxicol 1999; 19: 7–12.
27. McNaughton L, Puttagunta L, Martinez-Cuesta MA, et al. Distribution of nitric oxide synthase in normal and cirrhotic human liver. Proc Natl Acad Sci U S A 2002; 99: 17161–6.
28. Mohammed N, El-Alem S, Appleton I, et al. Expression of nitric oxide synthase isoforms in human liver cirrhosis. J Pathol 2003; 200: 647–55.
29. Ching-Mei H, Jyh-Seng W, Chao-Hsin L, et al. Kupffer cells protect liver from ischemia-reperfusion injury by an inducible nitric oxide synthase-dependent mechanism. Shock 2002; 17: 280–5.

30. Zhu W, Fung PC. The roles played by crucial free radicals like lipid free radicals, nitric oxide, and enzymes NOS and NADPH in CCl(4)-induced acute liver injury of mice. Free Radic Biol Med 2000; 29: 870–80.
31. Doğru-Abbasoğlu ve ark. Aminoguanidin ve N-asetilsisteinin endotoksemik sirozlu sıçanlarda karaciğer hasarı, oksidatif ve nitrozatif stres üzerine etkisi. Med J Kocatepe 2004; Ek sayı 27–32.
32. Beljaars E, Vos TA, Poelstra K, et. al. Expression of iNOS during development of liver fibrosis in rats. In: Wisse E, Knook DL and Balabaud C, Editors 1997. Cells of the Hepatic Sinusoid, volume 6 Leiden, The Netherlans; 32–3.
33. Mayoral P, Criado M, Hidalgo F, et al. Effect of chronic nitric oxide activation or inhibition on early hepatic fibrosis in rats with bile duct ligation. Clin Sci 1999; 96: 297–305.
34. Akarsu E, Okçu N, Akgöz K, et al. Serum nitric oxide in liver cirrhosis and its relation to blood pressure. Turk J Gastroenterol 1999; 10: 315–8.
35. Ahn B, Han BS, Kim DJ, et al. Immunohistochemical localization of inducible nitric oxide synthase and 3-nitrotyrosine in rat liver tumors induced by N-nitrosodiethylamine. Carcinogenesis 1999; 20: 1337–44.
36. Yuan GJ, Zhou XR, Gong ZJ, et al. Expression and activity of inducible nitric oxide synthase and endothelial nitric oxide synthase correlate with ethanol-induced liver injury. World J Gastroenterol 2006; 12: 2375–81.
37. Curran RD, Billiar TR, Stuehr DJ. Multiple cytokines are required to induce hepatocyte nitric oxide production and inhibit total protein synthesis. Ann Surg 1990; 212: 462–9.
38. Hon WM, Lee KH, Khoo HE. Nitric oxide in liver diseases: friend, foe, or just passerby? Ann N Y Acad Sci 2002; 962: 275–95.
39. Hogg N, Kalyanaraman B. Nitric oxide and lipid peroxidation. Biochim Biophys Acta 1999; 1411: 378–84.
40. Cristina E, Carnovale CS, Alveraz M, et al. Nitric oxide release and enhancement of lipid in regenerating rat liver peroxidation. J Hepatol 2000; 32: 798–804.
41. Muriel P. Nitric oxide protection of rat liver from lipid peroxidation, collagen accumulation, and liver damage induced by carbon tetrachloride. Biochem Pharmacol 1998; 56: 773–9.
42. Ozgocmen S, Ardicoglu O, Erdogan H, et al. In vivo effect of celecoxib and tenoxicam on oxidant/anti-oxidant status of patients with knee osteoarthritis. Ann Clin Lab Sci 2005; 35: 137–43.
43. Ezberci F, Bulbuloglu E, Ciragil P, et al. Intraperitoneal tenoxicam to prevent abdominal adhesion formation in a rat peritonitis model. Surg Today 2006; 36: 361–6.