EFFECT OF TENOXICAM ON BIOCHEMICAL SERUM PARAMETERS OF RATS

Bahar Göker, Ertuğrul Yurtsever and Azize Şener

Department of Biochemistry, Faculty of Pharmacy,
Marmara University, Tıbbiye Cad. 81010, Haydarpaşa, Istanbul,
Turkey

SUMMARY

Tenoxicam is a nonsteroidal analgesic of the oxicam group, which possesses both antipyretic and anti-inflammatory characteristics. The use of tenoxicam has recently increased and it is reported in the literature that treatments lasting between a few weeks to three months caused increases in serum alanine transferase (ALT), aspartate transferase (AST), gamma glutamyl transferase (GGT) and bilirubin in humans. Toxic dose treatments to rats caused alterations in renal parameters. To verify these observations, various biochemical parameters were examined following administration of nontoxic doses of tenoxicam to rats. Rats were divided into three groups. One group received tenoxicam 0.6 mg/kg/day; the second group received 1.2 mg/kg/day i.p. The control group received normal saline i.p. At the end of 15 days, blood samples from the animals' hearts were taken for routine biochemical tests. No statistically significant changes were observed in serum urea, uric acid, creatinine, electrolytes, ALT, AST, total protein, bilirubin or glucose levels between the treatment groups and control groups. Increases in GGT levels were found to be statistically significant in both of the treatment groups compared with the control group.

KEY WORDS

tenoxicam, biochemical parameters, gamma-glutamyl transferase, rat

INTRODUCTION

Tenoxicam, 4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1, 2-thiazine-3-carboxyamide-1,1-dioxide, is an anti-inflammatory drug with new oral nonsteroidal, analgesic and antipyretic properties /1/. Its analgesic and anti-inflammatory effects are stronger than acetylsalicylic acid, phenylbutazone and indomethacin. Like other nonsteroidal anti-inflammatory agents, it also blocks prostaglandin synthesis by inhibiting cyclooxygenase reversibly in the metabolism of aracidonic acid. It has no effect on lipooxygenase /2/. Its binding rate to plasma proteins is high. It is eliminated via the urine and bile via inactive 5′-hydroxy and 6-O-glucuronidate metabolites /3/.

In a previous study we investigated the effect of piroxicam on the serum parameters of rats. In the present study we investigated the effect of Tilcotil® (Roche) (the i.m./i.v. preparation of tenoxicam from the same group as piroxicam) at nontoxic doses on the biochemical serum parameters of rats. Tilcotil® is administered as a single daily dose of 20 mg.

MATERIALS AND METHODS

Wistar albino rats (Experimental Research and Animal Laboratory, Faculty of Medicine, Marmara University) weighing 180-200 g were used in this study. The animals were classified into three groups. Tenoxicam was injected into the first and second groups at doses of 0.6 mg/kg/day (n=7) and 1.2 mg/kg/day (n=7) i.p., respectively. The third group (control) (n=7) received physiological saline in the same volume. At the end of the 15th day, blood from the hearts was centrifuged and the serum was separated. Urea, uric acid, creatinine, electrolytes, alanine transferase (ALT), aspartate transferase (AST), gamma-glutamyl transferase (GGT), total protein, bilirubin, and glucose levels were determined by routine biochemical tests using a Hitachi 717 autoanalyser (Boehringer Mannheim).

RESULTS

In both treatment groups, serum urea, uric acid, creatinine, electrolytes, ALT, AST, total protein, bilirubin, and glucose levels were not found to be statistically significant from the control group

(Figs. 1-6). Serum GGT levels increased within normal limits in all animals treated with 0.6 mg/kg and 1.2 mg/kg tenoxicam. These findings were statistically significant ($0.05 > p > 0.02$) (Fig. 7).

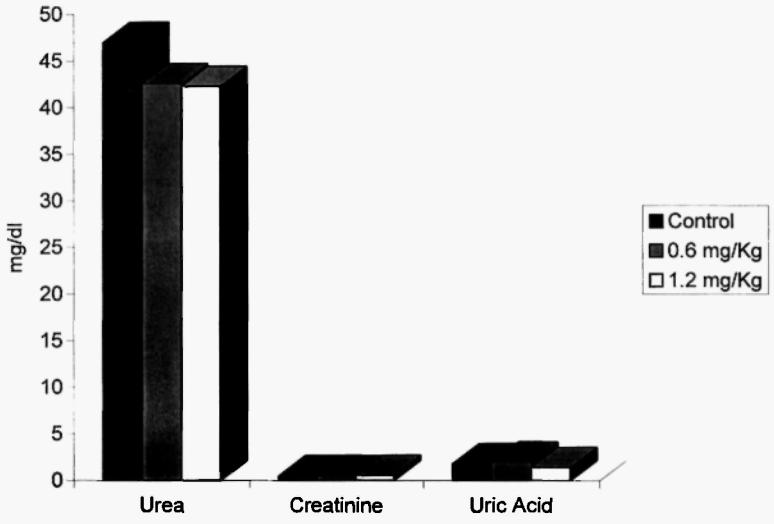

Fig. 1: The effect of tenoxicam on serum urea, uric acid and creatinine levels.

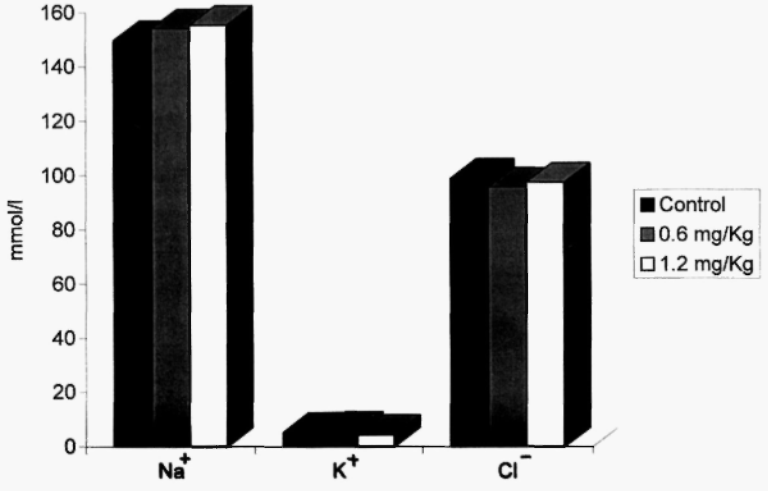

Fig. 2: The effect of tenoxicam on serum Na^+, K^+ and Cl^+ levels.

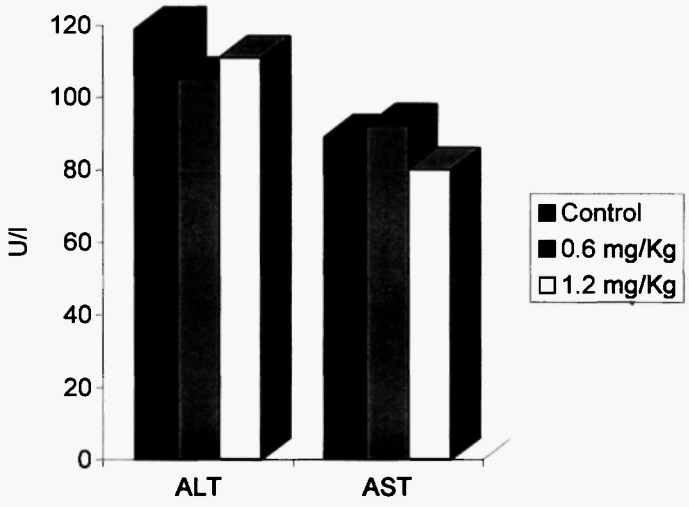

Fig. 3: The effect of tenoxicam on serum AST and ALT levels.

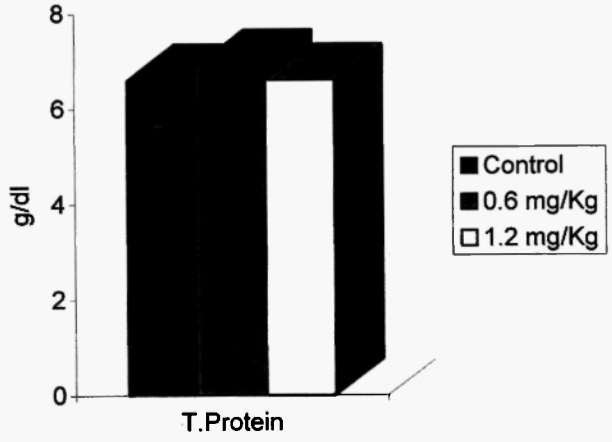

Fig. 4: The effect of tenoxicam on serum total protein levels.

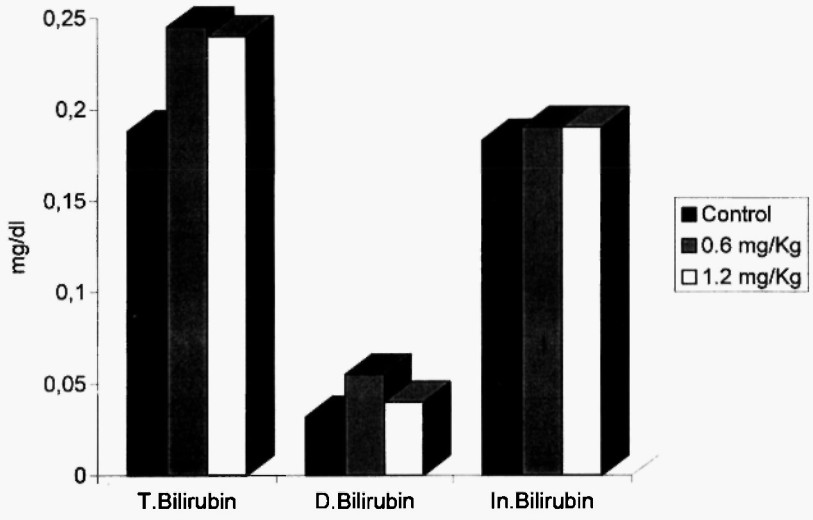

Fig. 5: The effect of tenoxicam on serum bilirubin levels.

Fig. 6: The effect of tenoxicam on serum glucose levels.

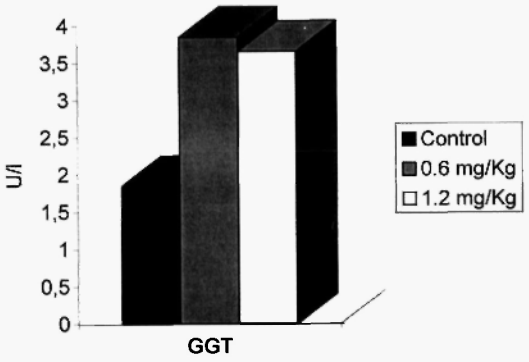

Fig. 7: The effect of tenoxicam on serum GGT levels

DISCUSSION

Since tenoxicam, one of the nonsteroidal anti-inflammatory drugs, has analgesic and antipyretic effects, it has been used to treat rheumatoid arthritis, osteoarthritis, tendonitis, trauma pain, dental pain and postoperative pain. It can be used in oral, rectal and parenteral forms /4/.

It also has some gastrointestinal side effects like other nonsteroidal anti-inflammatory agents. The ulcerogenic effects of tenoxicam have been found to be less than piroxicam and diclofenac sodium/5/.

In a previous study, it was observed that tenoxicam increased the plasma creatinine level in a patient with prerenal pathology /6/ and therefore its use in patients with renal failure was limited. No effect on glucose levels was observed /7/. In our present study, no changes in the urea, uric acid, creatinine or glucose levels were observed in the rats which received tenoxicam (0.6 mg/kg/day or 1.2 mg/kg/day) for 15 days compared to the control groups.

Increased levels of ALT and bilirubin have been observed in patients treated with nonsteroidal anti-inflammatory drugs for a period of a few weeks to three months /8/. In our study, no significant difference was observed in the AST and ALT levels with the doses used. However, it was also demonstrated that the GGT level increased significantly within normal limits in the rats receiving tenoxicam (0.1-2

mg/kg). It has been known that some drugs and alcohol increase the serum GGT level, depending on the extent of liver microsomal enzyme induction tissue damage /9/.

Salicylates have been known to cause hepatic disorders dose dependently and to change serum AST and ALT values /10/. In a previous study on acetylsalicylic acid in rats, no significant change in serum GGT level was observed in high doses. However, in the same study, the liver plasma membrane GGT was increased considerably. This was attributed to the possibility that acetylsalicylic acid might cause liver toxicity /11/.

In a previous study in our laboratory, the effect of piroxicam on biochemical serum parameters in rats in normal therapeutic doses was investigated and a significant increase in GGT levels was demonstrated. It was within the limits of normal values at a dose of 2 mg/kg /12/. In this study of tenoxicam at non-toxic doses, we observed the same significant change. This change might be a result of microsomal enzyme induction or a toxic effect on the liver or other organ.

REFERENCES

1. Al-Ghamdi MS, Dissanayake AS, Cader ZA, Jain S. Tenoxicam-induced gastropathy in the rat: a comparison with piroxicam and diclofenac sodium, and the inhibitory effects of ranitidine and sucralfate. J Intern Med Res 1991; 19: 242-248.
2. Micheli L, Giorgi G, Fiaschi AI, Ceratani D. Relationship between piroxicam content and glutathione levels in rat brain. Pharmacol Res 1990; 22 (Suppl 1): 31-33.
3. Nilsen OG. Clinical pharmacokinetics of tenoxicam. Clin Pharmacokinet 1994; 26: 16-43.
4. Todd PA, Clissold SD. Tenoxicam. An update of its pharmacology and therapeutic efficacy in rheumatic diseases. Drugs 1991; 41: 625-646.
5. Muller P, Dammann HG, Leucht U. Comparison of the gastroduodenal tolerance of tenoxicam and diclofenac Na. Eur J Clin Pharmacol 1989; 36: 419-421.
6. Heinti RC. Tenoxicam and renal function. Drug Safety 1995; 12: 110-119.
7. Day RO, Geislinger G, Paull D, Williams KM. The effect of tenoxicam on tolbutamide pharmacokinetics and glucose concentrations in healthy volunteers. Int J Clin Pharmacol Ther 1995; 33 :308-310.
8. Sherman EK, Jones C. Hepatotoxicity associated with piroxicam use. Gastroenterology 1992; 103: 354-356.
9. Rosalki SB, Tarlow D, Rau D. Plasma gamma-glutamyl transpeptidase

elevation in patients receiving enzyme inducing drugs. Lancet 1971; ii: 367-377.

10. Beyhan Ö, Eryürek F, Öner P, Baysal K. Liver γ glutamyl transpeptidase activity following chronic treatment with acetylsalicylic acid in rats. Enzyme 1989; 42: 185-188.
11. Nakagawa M, Ishihara N, Shimokawa T, Kojima S. Effect of clofibrate on lipid peroxidation in rats treated with aspirin and 4-pentenoic acid. J Biochem 1987; 101: 81-88.
12. Yurtsever E, Yaman A, Göker B, Gümüş A, Yardımcı T. Piroksikamın ratlarda bazı biyokimyasal serum parametrelerine etkisi. MÜ Eczacılık Dergisi, 1997; 13: 27-35.