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Effects of Tolfenamic Acid on Oxidative Status, Serum Biochemical, and Hemogram Parameters in Rats

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ABSTRACT

***Background*:** Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used group of drugs. Tolfenamic acid is an NSAID with analgesic, anti-inflammatory, and anti-pyretic properties. It exerts its effect by inhibiting prostaglandin synthesis. Considering that NSAIDs may affect oxidative status, liver and kidney function, and hemogram parameters, it was hypothesized in this study that the administration of tolfenamic acid at different doses may affect serum oxidative status, liver and kidney function, and hemogram parameters. The aim of the study is to investigate the effects of tolfenamic acid at different doses on serum oxidative status, biochemical, and hemogram parameters.

***Materials, Methods & Results*:** In the study, 24 healthy female Wistar-Albino rats were equally divided into 4 groups. No treatment was administered to the control group, while the other 3 groups were administered 4, 10, and 20 mg/kg tolfenamic acid intramuscularly for 2 days, respectively. Twenty-four h after the last administration, the animals were anesthetized, blood samples were collected and they were then euthanized. The levels of oxidative status parameters (8-hydroxy-2-deoxyguanosine, malondialdehyde, superoxide dismutase, glutathione peroxidase) in the serum samples were measured using an ELISA reader. Serum aspartate aminotransferase, gamma glutamyl transferase, blood urea nitrogen, cholesterol, calcium, phosphorus, and magnesium levels were measured by using an autoanalyzer, and hemogram parameters (white blood cell, red blood cell, platelet, hemoglobin, hematocrit) were measured by using a hemocell counter. 8-hydroxy-2-deoxyguanosine and glutathione peroxidase levels in the group to which 20 mg/kg tolfenamic acid were higher ($P < 0.05$) than in the other 3 groups. Lower aspartate aminotransferase and high white blood cell levels in the control group were determined ($P < 0.05$) than the 20 mg/kg group. Statistical fluctuations ($P < 0.05$) were observed in red blood cell levels.

***Discussion*:** 8-hydroxy-2-deoxyguanosine, a biomarker for oxidative damage in DNA, and glutathione peroxidase, antioxidant enzyme, levels of the highest dose (20 mg/kg) of tolfenamic acid group were higher than control, 4 mg/kg, and 10 mg/kg groups. This may be due to tolfenamic acid causing DNA damage. The high glutathione peroxidase level may be dependent on tolfenamic acid increased formation of hydrogen peroxide. However, no research could be found regarding the effect of tolfenamic acid on oxidative stress in healthy individuals. Considering the results of the present study, it is understood that NSAID tolfenamic acid does not cause oxidative stress at the recommended doses, but it may cause oxidative stress at the DNA level depending on the dose. Increased aspartate aminotransferase, a marker of liver damage, levels in the highest dose (20 mg/kg) of tolfenamic acid group, were determined. It is known that NSAIDs including tolfenamic acid can cause hepatotoxicity. Elevated liver enzymes may be detected in patients using NSAIDs and enzyme levels should be monitored in patients using NSAIDs. Hence, tolfenamic acid administered at the recommended doses may not cause hepatotoxicity. Hemogram values are used for the diagnosis of selected diseases but occasionally for monitoring the side effects of drugs. Reduced white blood cell and red blood cells count in tolfenamic acid at a dose of 20 mg/kg group that may be related to NSAID caused bleeding. Tolfenamic acid at the recommended doses has no effect on hemogram parameters. However, tolfenamic acid may affect hemogram parameters related to dose. In conclusion, it can be asserted that high-dose tolfenamic acid may cause oxidative stress and liver damage and may reduce hemogram parameters.

Keywords: tolfenamic acid, oxidative status, biochemical values, hemogram.

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INTRODUCTION

Tolfenamic acid, a potent non-steroidal anti-inflammatory drug (NSAID), is recommended to use a dose of 2-4 mg/kg (IM, IV, SC, SID, up to 3 d). It is used in veterinary medicine for bone-joint and muscle system pain and for elevated body temperature associated with infectious diseases [23,24].

The effects of different NSAIDs on oxidative status have been previously investigated [7,12]. During energy production in living organisms, oxygen-derived free oxygen radicals are continuously produced. The superoxide dismutase (SOD) enzyme combines 2 superoxide radicals with 2 hydrogen atoms to convert them into hydrogen peroxide. The glutathione peroxidase (GPX) enzyme converts hydrogen peroxide into water and molecular oxygen. If free oxygen radicals cannot be sufficiently converted into ineffective structures, lipid peroxidation develops [22,25]. Malondialdehyde (MDA) forms as a result of lipid peroxidation, and the MDA level is a biomarker used to figure out cellular damage [20,25]. During the repair of oxidative stress-induced DNA damage, 8-hydroxy-2-deoxyguanosine (8-OHDG) forms and is the most widely accepted biomarker for determining oxidative stress-related DNA damage [11]. Drugs used in treatment may cause unwanted or side effects at recommended doses, as well. Measuring some parameters from blood, serum or plasma provides information about the affected systems or organs [13,16].

The aim of the study is to determine the effect of administering different doses of tolfenamic acid to rats on serum oxidative status, liver and kidney function parameters, serum elements, cholesterol, and hemogram parameters.

MATERIALS AND METHODS

Animals and experimental design

In the study, 24 healthy female Wistar-Albino rats (10-12 weeks, 260-290 g) were used. The rats were housed at room temperature (25 ºC), in a 12-h dark/light cycle, at 50-55% relative humidity at Selçuk University Experimental Medicine Research and Application Center. Food and water were provided ad libitum. A total of 24 rats were equally divided into 4 groups. No administration was performed on the control group (n:6), while the other 3 groups received intramuscular injections of tolfenamic acid[1] [Tolfenak® - at doses of 4 (n:6), 10 (n:6), and 20 (n:6) mg/kg for 2 days, respectively]. Twenty-four h after the last administration, the animals were anesthetized with a combination of xylazine[2] [Xylazin Bio® - 8 mg/kg, IP] + ketamine[3] [Ketasol® - 75 mg/kg, IP]. Under anesthesia, blood was collected from the hearts of the animals, and then they were euthanized using the cervical dislocation method. Blood was collected into K3-EDTA tubes for measurement of hemogram parameters. The collected blood samples were centrifuged[4] (Sigma 3K18) at 1500 *g* for 10 min to separate the serum fractions.

ELISA, serum biochemical and hemogram analysis

In the study, rat-specific ELISA kits[5] obtained from a commercial company were used to measure serum oxidative stress parameters 8-OHDG, MDA, SOD, and GPX using an ELISA reader[6]. Serum levels of aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), blood urea nitrogen (BUN), cholesterol, calcium, phosphorus, and magnesium were measured using an autoanalyzer[7], while hemogram parameters (White blood cell, red blood cell, platelet, hemoglobin, hematocrit) were measured using a hemocell counter[8] (Abbott Cell-Dyn 3700 Hematology Analyzer).

Statistical analysis

Research results are given as mean ± standard error (SE). Data were compared using ANOVA and post-hoc DUNCAN tests (SPSS 29.0[9]). The value of $P < 0.05$ was accepted as statistically significance level.

RESULTS

Table 1 shows the effect of different doses of TA on serum oxidative stress parameters. While the group with highest-dose (20 mg/kg) TA showed higher levels of 8-OHDG and GPX than the other groups ($P < 0.05$), no statistical change was determined in MDA and SOD levels ($P > 0.05$).

Table 2 shows the effect of TA on different doses on serum biochemical parameters. AST level elevated in the 20 mg/kg TA group ($P < 0.05$), while no statistically significant change was determined in other parameters ($P > 0.05$).

Table 3 shows the effect of TA at different doses on hemogram parameters. WBC levels lowered in the 20 mg/kg TA group compared to the control group ($P < 0.05$), while a statistically significant fluctuation was determined in RBC values ($P < 0.05$). No statistically significant changes were observed ($P > 0.05$) in other hematological parameters (Platelet, hemoglobin, hematocrit).

Table 1. The effect of different doses of tolfenamic acid (4, 10, and 20 mg/kg, IM, SID, 2 days) on serum oxidative stress parameters (mean ± SE).

Parameters	Control (n = 6)	4 mg/kg (n = 6)	10 mg/kg (n = 6)	20 mg/kg (n = 6)
8-OHDG ng/mL	1.49 ± 0.17[b]	1.79 ± 0.12[b]	1.47 ± 0.19[b]	2.67 ± 0.30[a]
MDA nmol/mL	0.79 ± 0.11	0.93 ± 0.08	0.88 ± 0.08	0.94 ± 0.20
SOD ng/mL	1.40 ± 0.14	1.49 ± 0.12	1.41 ± 0.10	1.69 ± 0.21
GPX pg/mL	359.11 ± 8.75[b]	379.22 ± 13.15[b]	366.21 ± 7.63[b]	432.99 ± 18.53[a]

[a,b]Different letters in the same line are statistically significant ($P < 0.05$). 8-OHDG: 8-Hydroxy-2-deoxyguanosine; MDA: Malondialdehyde; SOD: Superoxide dismutase; GPX: Glutathione peroxidase.

Table 2. The effect of different doses of tolfenamic acid (4, 10, and 20 mg/kg, IM, SID, 2 days) on serum biochemical parameters (mean ± SE).

Parameters	Control (n = 6)	4 mg/kg (n = 6)	10 mg/kg (n = 6)	20 mg/kg (n = 6)
AST U/L	54.83 ± 3.28[b]	94.00 ± 18.44[ab]	106.33 ± 16.16[ab]	110.66 ± 23.67[a]
GGT U/L	7.16 ± 0.16	6.83 ± 0.16	6.83 ± 0.16	7.00 ± 0.00
BUN mg/dL	12.83 ± 0.65	12.50 ± 1.78	13.83 ± 1.40	15.16 ± 1.10
Chol mg/dL	45.55 ± 4.51	61.52 ± 11.48	60.73 ± 8.13	66.48 ± 6.23
Ca mg/dL	5.92 ± 0.49	6.11 ± 1.05	6.15 ± 0.62	6.42 ± 0.60
P mg/dL	4.69 ± 0.33	4.90 ± 0.53	5.25 ± 0.47	5.17 ± 0.59
Mg mg/dL	1.70 ± 0.16	1.70 ± 0.27	1.76 ± 0.21	2.25 ± 0.34

[a,b]Different letters in the same line are statistically significant ($P < 0.05$). AST: Aspartate aminotransferase; GGT: Gamma glutamyl transferase; BUN: Blood urea nitrogen; Chol: Cholesterol; Ca: Calcium; P: Phosphorus; Mg: Magnesium.

Table 3. The effect of different doses of tolfenamic acid (4, 10, and 20 mg/kg, IM, SID, 2 d) on hemogram parameters (mean ± SE).

Parameters	Control (n = 6)	4 mg/kg (n = 6)	10 mg/kg (n = 6)	20 mg/kg (n = 6)
WBC $x10^9$/L	11.18 ± 0.82[a]	10.14 ± 1.04[ab]	8.35 ± 0.96[ab]	7.25 ± 1.60[b]
RBC $x10^{12}$/L	6.72 ± 0.14[ab]	6.84 ± 0.13[a]	6.71 ± 0.18[ab]	5.25 ± 0.91[b]
PLT $x10^9$/L	678.83 ± 59.80	669.66 ± 10.81	624.83 ± 15.79	513.33 ± 103.56
Hgb g/dL	12.86 ± 0.34	13.21 ± 0.21	12.71 ± 0.39	10.40 ± 1.81
Htc %	35.80 ± 0.86	36.46 ± 0.50	35.31 ± 0.78	29.01 ± 5.01

[a,b]Different letters in the same line are statistically significant ($P < 0.05$). WBC: White blood cell counts; RBC: Red blood cell counts; PLT: Platelet counts; Hgb: Hemoglobin; Htc: Hematocrit.

DISCUSSION

Tolfenamic acid, which is a member of the fenamate group, is used in veterinary medicine for metabolic pain and infectious diseases [23], while it is used for the treatment of acute migraine attacks, dysmenorrhea, osteoarthritis and rheumatoid [2]. Although the drug is recommended for short-term use (2 or 4 days), even its short-term use can cause side effects, particularly related to the gastrointestinal system [23,24].

In the study, the highest dose (20 mg/kg) of TA administration was found to be higher ($P < 0.05$) than the control, 4 mg/kg, and 10 mg/kg groups in terms of 8-OHDG and GPX levels (Table 1). MDA, that forms as a result of lipid peroxidation [25], is accepted as a biomarker used in the evaluation of cellular damage [20,25]. The measurement of 8-OHDG level is used as a biomarker for oxidative damage in DNA [11]. Hydrogen peroxide produced by the SOD enzyme is inactivated by the GPX enzyme [22,25]. In the present study, the high GPX level determined in the 20 mg/kg TA group may be due to the fact that TA increased formation of hydrogen peroxide. No study could be found regarding the effect of TA on oxidative stress in healthy living organisms. However, a study conducted in cell culture reported that the effects of TA at high concentrations can inhibit the superoxide radical produced by neutrophils, but this may not be clinically significant in terms of the anti-inflammatory effect of TA at therapeutic doses [14]. On the other hand, it has been stated that TA may exhibit antioxidant effects [18] and TA complexes with copper (II) may be effective superoxide scavengers [17]. However, it has been determined that TA exerts a positive effect by inducing apoptosis through the production of free oxygen radicals in cancer [8,19]. It has been reported that diclofenac sodium, ibuprofen, flurbiprofen, and paracetamol lower MDA levels and may inhibit lipid peroxidation, but celecoxib and indomethacin cause an increase in MDA levels and may lead to lipid peroxidation [7]. It has been stated that diclofenac, meloxicam, or celecoxib lower MDA levels in patients with rheumatoid arthritis and these drugs may exhibit antioxidant effects to varying degrees [12]. It has been reported that oral administration of phenylbutazone at different doses to horses reduces antioxidant capacity in the gastric mucosa and elevates MDA levels [3]. Considering the results of the present study, it is understood that NSAID drugs do not have similar effects on oxidative status and may have different effects in patients or healthy individuals. The results of the study suggest that TA does not cause oxidative stress at the recommended doses, but it may cause oxidative stress at the DNA level depending on the dose.

In the present study, it was observed that AST levels, a marker of liver damage, elevated in a dose-dependent manner, and the AST level in the group receiving the highest dose (20 mg/kg) was statistically different ($P < 0.05$) from that in the control group (Table 2). It is known that NSAIDs [15,21] and TA can cause hepatotoxicity [2]. Elevated liver enzymes may be observed in patients using NSAIDs and enzyme levels should be monitored in patients using NSAIDs for a long time [9]. It has been determined that TA at a dose of 100 mg/kg [PO, SID, 6 days] to mice caused lymphocyte infiltration in the portal canal of the liver, congestion and dilation in the sinusoids, and accumulation in Kupffer cells [26]. However, it has been reported that administration of TA at different doses [2, 4, and 8 mg/kg, IV] to goats [6] and ducks [10] did not affect AST levels. According to the present study, it can be stated that TA administered at the recommended doses may not cause hepatotoxicity, or nephrotoxicity and may not affect cholesterol and serum element (calcium, phosphorus, magnesium) levels but may cause liver damage at high doses.

In the present study, it was determined that TA at a dose of 20 mg/kg lowered WBC and RBC levels ($P < 0.05$). However, no statistically significant difference was observed in platelet, hemoglobin, and hematocrit levels ($P > 0.05$) [Table 3]. Hemogram data are used for the diagnosis of certain diseases and sometimes for monitoring the side effects of drugs [5]. In general, NSAIDs can cause ulcers and bleeding in the gastrointestinal system [1,4]. This condition is associated with platelet inhibition [15]. According to the present study, it can be stated that TA at the recommended doses has no effect on hemogram parameters, but it may affect hemogram parameters due to its dose-related bleeding or its effect on bone marrow.

CONCLUSION

It can be stated that TA, which is a potent NSAID, does not cause oxidative stress, does not affect liver and kidney functions, and has no effect on serum cholesterol and element levels or hemogram parameters at recommended doses. However, it can be stated that even for very short periods, its administration at high doses may cause oxidative stress and hepatotoxicity and may lower levels of hemogram parameters.

MANUFACTURERS

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***Ethical approval*.** Research protocol was approved by Experimental Medicine Application and Research Center Animal Experiments Local Ethics Committee of Selcuk University (SUDAM, 2025/102).

***Artificial Intelligence Statement*.** The authors declare that no artificial intelligence (AI) tools were used to generate, analyze, or interpret the data or to produce the scientific content of this manuscript. The authors are solely responsible for all aspects of the work.

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of paper.

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