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Effect of menbutone on oxidative stress in sheep

Efecto de la menbutona sobre el estrés oxidativo en ovejas

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ABSTRACT

The objective of this research was to determine the effects of administering the choleretic-effective menbutone (genabilic acid) at the recommended dose and duration of serum oxidative status and biochemical parameter levels in sheep. As is known, changes in the oxidative status of living organisms can be observed in many drug applications, disease states, or metabolic disorders. In the study, menbutone was administered at a dose of 10 mg·kg^{-1} (slow IV, SID, 2 days) to 10 Central Anatolian Merino sheep. Blood samples were collected from the sheep before (0th hour) and at the 12th, 24th, and 48th hours after menbutone administration. Serums were obtained from the collected blood samples. Serum oxidative status parameters (8–hydroxy–2–deoxyguanosine, malondialdehyde, superoxide dismutase, glutathione peroxidase, catalase), troponin I, and creatine kinase-MB isoenzyme levels were measured using the ELISA method, while levels of serum routine biochemical parameters were measured using an autoanalyzer. Menbutone did not affect oxidative stress parameters (8–hydroxy–2–deoxyguanosine, malondialdehyde, superoxide dismutase, glutathione peroxidase, catalase) in sheep (P>0.05) but caused temporary increases (P<0.05) in serum triglyceride and cholesterol levels. However, no statistically significant changes were detected in other serum biochemical parameters (Troponin I, creatine kinase-MB isoenzyme, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, low-density lipoprotein, high-density lipoprotein, blood urea nitrogen, creatinine). In conclusion, it can be asserted that menbutone can be used safely in sheep without altering oxidative stress parameters, but monitoring serum triglycerides and cholesterol may be important in animals with metabolic disorders.

Key words: Menbutone; oxidative status; biochemical parameters; sheep

RESUMEN

El objetivo de esta investigación fue determinar los efectos de la administración de menbutona (ácido genabilico), con efecto colerético, en la dosis recomendada y la duración del estado oxidativo sérico y los niveles de parámetros bioquímicos en ovejas. Como se sabe, los cambios en el estado oxidativo de los organismos vivos se pueden observar en muchas aplicaciones de fármacos, enfermedades o trastornos metabólicos. En el estudio, se administró menbutona en una dosis de 10 mg·kg^{-1} (IV lenta, SID, 2 días) a 10 ovejas merinas de Anatolia central. Se recogieron muestras de sangre de las ovejas antes (hora 0) y a las 12, 24 y 48 horas después de la administración de menbutona. Se obtuvieron sueros de las muestras de sangre recogidas. Los parámetros séricos del estado oxidativo (8–hidroxi–2–desoxiguanosina, malondialdehído, superóxido dismutasa, glutatión peroxidasa, catalasa), troponina I y los niveles de isoenzima MB de la creatina quinasa se midieron mediante el método ELISA, mientras que los niveles de parámetros bioquímicos séricos de rutina se midieron utilizando un autoanalizador. La menbutona no afectó los parámetros de estrés oxidativo (8–hidroxi–2–desoxiguanosina, malondialdehído, superóxido dismutasa, glutatión peroxidasa, catalasa) en ovejas (P>0,05), pero causó aumentos temporales (P<0,05) en los niveles séricos de triglicéridos y colesterol. Sin embargo, no se detectaron cambios estadísticamente significativos en otros parámetros bioquímicos séricos (troponina I, isoenzima MB de la creatina quinasa, fosfatasa alcalina, aspartato aminotransferasa, alanina aminotransferasa, lipoproteínas de baja densidad, lipoproteínas de alta densidad, nitrógeno ureico en sangre, creatinina). En conclusión, se puede afirmar que la menbutona puede usarse de forma segura en ovejas sin alterar los parámetros de estrés oxidativo, pero la monitorización de los triglicéridos y el colesterol séricos puede ser importante en animales con trastornos metabólicos.

Palabras clave: Menbutona; estado oxidativo; parámetros bioquímicos; ovejas

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INTRODUCTION

Menbutone (genabilic acid) is a drug licensed for use in the Veterinary field for the treatment of metabolic diseases related to the digestive system and liver in horses (*Eqqus caballus)*, cattle (*Bos taurus*), sheep (*Ovis aries*), goats (*Capra hircus*), and pigs (*Sus scrofa domesticus*) for choleretic purposes. Although the mechanism of action of the drug is not clearly known, it has been reported that it may exert its effect by stimulating the parasympathetic nervous system [1, 2].

The general dosage of the drug in target species is 10 mg·kg^{-1} administered intramuscularly (IM) or intravenously (IV). Menbutone causes a 2 to 5–fold increase in bile, liver, stomach, and pancreatic secretions after its administration. It directly stimulates liver parenchymal cells, initiating the secretion of bile in its normal composition and in abundant quantities. This improves digestive and liver function in patients [2, 3].

The use of the drug is not recommended in patients with heart disease and in the late stages of pregnancy. Drug may cause some adverse effects such as restlessness, salivation, lacrimation, tremors, involuntary defecation and urination, inability to stand during rapid intravenous administration, as well as necrosis, edema, and hemorrhage at the injection site in target species. When administered at high doses to rodents, it has been determined that it may cause cyanosis, respiratory depression, nephrotoxic and hepatotoxic effects [1, 3].

Menbutone increases bile secretion in the liver [1], and it has been reported bilirubin exerts an antioxidant effect by scavenging or neutralizing free radicals. Bile acids, produced in the liver, can indirectly exert an antioxidant effect by facilitating the absorption of vitamins such as A and E from the intestines. Furthermore, bile acids can exhibit antioxidant effects by trapping oxygen free radicals within bile acid micelles [4]. Free oxygen radicals are the most produced substances in living organisms, and these harmful structures are converted into harmless structures by enzymatic (superoxide dismutase, catalase, glutathione peroxidase, enter other) [5], and/or non-enzymatic substances (vitamin C, vitamin E, vitamin A, glutathione, etc.) [6].

Specifically, an oxygen molecule that accepts an electron during the mitochondrial respiratory chain forms the superoxide radical. The superoxide dismutase (SOD) enzyme found in cells combines two superoxide radicals with two hydrogen atoms to form hydrogen peroxide. Then hydrogen peroxide is transformed into molecular oxygen and water by the enzymes glutathione peroxidase (GPX) and catalase (CAT), turning it into harmless molecules [5].

There is an equilibrium between antioxidants and oxidants in living organisms. A disruption of this balance in favor of oxidant substances is defined as oxidative stress. Non-neutralized free oxygen radicals attack structures in cells such as lipids, proteins, and DNA, causing damage to these structures. Lipids in the cell membrane are highly sensitive to free oxygen radicals, and damage to this structure is defined as lipid peroxidation [5]. Lipid peroxidation produces malondialdehyde (MDA) and determination of MDA level is used to understand the degree of cellular damage [7].

Malondialdehyde has mutagenic, cytotoxic, and carcinogenic properties. MDA can also inhibit the functions of antioxidant enzymes associated with protecting cells against oxidative stress [8]. 8–hydroxy–2–deoxyguanosine (8–OHDG), produced during the repair of DNA injury caused by oxidative stress, is considered as the most common biomarker of DNA damage [9] and has mutagenic potential [10].

It has been suggested that some drugs causing oxidative stress may cause heart damage and that markers of heart damage, such as troponin I and creatine kinase-MB isoenzyme (CK-MBiso) in serum, may increase [11, 12, 13].

Although sheep are defined as the target species in the use of menbutone [14], there is very limited number of studies on its effect on organ damage biomarkers in sheep. It is known that drugs used in treatment may cause some undesirable or side effects at the recommended doses, in addition to their therapeutic effects in living organisms. Drug-induced undesirable or side effects can be clinically observed and can also be identified by measuring certain parameters in the blood [15].

The levels of these analyzed parameters allow us to understand the damage developing in the systems or organs of living organisms [15, 16]. CK-MB isoenzyme and troponin I levels are associated with heart damage [17, 18], while creatinine and blood urea nitrogen (BUN) levels provide information about kidney function [19].

While serum alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels provide information about liver and bile duct function [20], triglyceride, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels provide information about lipid metabolism [21].

Given that menbutone, which has a choleretic effect, increases bile secretion [1, 14], may affect the oxidative mechanisms of bile content [4] and may cause serum biochemical values at recommended therapeutic doses and duration, it was hypothesized that the administration of menbutone to sheep may affect serum oxidative status and biochemical values.

The objective of this study was to determine the effect of menbuton administration in sheep on oxidative stress markers (8–OHdG, MDA, SOD, GPX, and CAT), cardiac (troponin I, CK-MBiso), hepatic (ALP, ALT, AST), and renal (BUN, creatinine) functions, alongside lipid profile parameters (cholesterol, triglycerides, HDL, LDL). Hence, this study will determine the drug's safety in sheep, in addition to its effect on the oxidative status.

MATERIALS AND METHODS

Experimental design and animal applications

The study was conducted on 10 Central Anatolian Merino sheep (2–3 years old, 50–55 kg). The procedure of the study was approved by the Ethics Committee of the Selcuk University Faculty of Veterinary Medicine Experimental Animal Production and Research Center (SUVDAMEK) (2025/63).

Menbutone (Bavet Menbutone inj., Bavet Ilac Sanayi, Istanbul, Türkiye) was administered to the sheep at a dose of 10 mg·kg^{-1}

[slow IV, once daily (SID)] for 2 days (d). To minimize variations due to individual differences, no separate control group was established in the study. Instead, blood was collected from all animals 0 hours (h) before treatment and assessed as a self-control group.

Blood samples were taken from the jugular veins of the sheep before administration (0^{th} h) and at 12^{th}, 24^{th}, and 48^{th} hours after the first administration. To isolate serum from the collected blood samples, they were centrifugated (Sigma 3K18, Osterode am Harz, Germany) at 4000 g for 10 minutes and kept at – 80 °C (Operon Co Ltd Ultra Low Temperature, South Korea) until biochemical measurements.

ELISA and blood serum biochemical analyses

Commercial ELISA kits (BT-LAB, Zhejiang, China) were used in the study, and all kits were selected to be specific to sheep. Serum 8–OHDG, MDA, SOD, GPX, CAT, troponin I, and CK-MBiso levels were measured using ELISA kits and an ELISA plate reader (MWGt Lambda Scan 200; Bio-Tec Instruments, Winooski, VT, USA) according to the kit instructions.

Serum AST, ALT, ALP, cholesterol, triglycerides, HDL, LDL, BUN, and creatinine levels were determined using an autoanalyzer (BT–3000 plus, Biotecnica Instruments, Rome, Italy).

Statistical analysis

Research results are given as mean ± standard error (SE) and were compared amongst groups and time points using ANOVA and post-hoc TUKEY tests (SPSS 29.0). The value of $P<0.05$ was accepted as statistically significance level.

RESULTS AND DISCUSSION

TABLE I shows the effect of menbutone administration on oxidative stress parameters (SOD, GPX, CAT, MDA, 8–OHDG) in sheep, while TABLE II shows its effects on biochemical parameters (Troponin I, CK-MBiso, AST, ALT, ALP, cholesterol, triglyceride, HDL, LDL, BUN, creatinine). Menbutone administration had no effect on oxidative stress parameters in sheep ($P>0.05$). Menbutone caused a temporary increase in triglyceride and cholesterol levels in sheep ($P<0.05$), but no effect on heart, liver, and kidney function parameters was detected ($P>0.05$). Furthermore, no clinically adverse effects (fever, salivation, convulsions, decreased appetite, discomfort, etc.) were observed in the animals during the application period.

Menbutone is used in sheep for choleretic purposes in the treatment of metabolic diseases related to the digestive system and liver. The drug causes an increase in bile, liver, stomach, and pancreatic secretions, exerting a regulatory effect on digestive and liver functions. General dosage of the menbutone in sheep is 10 mg·kg^{-1} (IM or IV) [2, 3].

However, menbutone may restlessness, salivation, lacrimation, tremors, involuntary defecation and urination, etc. as side effects [1, 2, 3]. Although the drug has been used for a long time in target species and the bile acids and bilirubin it causes to be secreted are known to exhibit antioxidant effects, there are insufficient reports on its effects on oxidative status values and heart, liver, and kidney function parameters in healthy sheep. Furthermore, there is limited data on its direct effects on lipid metabolism parameters in sheep.

TABLE I
The effect of menbutone (10 mg·kg^{-1}, slow intravenously, single in a day, 2 days) on serum oxidative status parameters in ten sheep (Mean ± Standard error)*

Parameters	0^{th} hour	12^{th} hour	24^{th} hour	48^{th} hour
SOD ng·mL^{-1}	64.63 ± 5.25	63.10 ± 4.99	75.17 ± 7.02	66.14 ± 4.75
GPX nU·mL^{-1}	606.48 ± 118.05	483.81 ± 79.50	544.81 ± 94.98	434.77 ± 67.33
CAT ng·mL^{-1}	3.17 ± 0.60	3.61 ± 0.57	3.63 ± 0.64	3.24 ± 0.62
MDA nmol·L^{-1}	5.09 ± 0.82	4.18 ± 0.66	5.52 ± 1.16	3.79 ± 0.55
8–OHDG ng·mL^{-1}	5.53 ± 0.95	4.84 ± 0.58	5.58 ± 0.75	4.65 ± 0.68

SOD: Superoxide dismutase, GPX: Glutathione peroxidase, CAT: Catalase, MDA: Malondialdehyde, 8–OHDG: 8–hydroxy–2–deoxyguanosine. *: No statistical difference was found in the data in the same row (ANOVA, Tukey test, $P>0.05$)

TABLE II
The effect of menbutone (10 mg·kg^{-1}, slow intravenously, single in a day, 2 days) on serum biochemistry parameters in ten sheep (Mean ± Standard error)

Parameters	0^{th} hour	12^{th} hour	24^{th} hour	48^{th} hour
Troponin I ng·mL^{-1}	121.81 ± 27.81	192.81 ± 34.80	139.43 ± 31.04	118.97 ± 16.43
CK-MBiso ng·mL^{-1}	0.67 ± 0.11	0.67 ± 0.08	0.63 ± 0.09	0.58 ± 0.07
ALP U·L^{-1}	49.50 ± 15.17	101.70 ± 38.15	48.90 ± 16.33	74.00 ± 31.15
AST U·L^{-1}	97.90 ± 4.19	100.50 ± 4.05	94.80 ± 4.51	94.70 ± 4.32
ALT U·L^{-1}	187.40 ± 33.10	174.50 ± 36.26	193.20 ± 34.93	172.80 ± 38.44
Cholesterol mg·dL^{-1}	67.20 ± 2.85^{ab}	73.40 ± 2.14^{a}	64.80 ± 2.71^{ab}	61.50 ± 3.59^{b}
Triglyceride mg·dL^{-1}	16.10 ± 1.79^{b}	38.40 ± 2.36^{a}	19.70 ± 2.34^{b}	17.40 ± 2.04^{b}
LDL mg·dL^{-1}	13.50 ± 0.80	13.00 ± 1.09	11.30 ± 0.91	11.30 ± 1.21
HDL mg·dL^{-1}	32.80 ± 1.20	33.71 ± 1.62	31.99 ± 1.62	31.20 ± 1.75
BUN mg·dL^{-1}	12.18 ± 0.41	10.48 ± 0.35	10.65 ± 0.69	12.40 ± 0.53
Creatinine mg·dL^{-1}	0.91 ± 0.04	0.97 ± 0.04	0.88 ± 0.03	0.91 ± 0.03

CK-MBiso: Creatine kinase-MB isoenzyme, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BUN: Blood urea nitrogen. ^{a,b}: Different letters in the same row are statistically significant (ANOVA, Tukey test, $P<0.05$)

The effect of menbutone on some oxidative stress serum parameters in sheep were investigated in sheep which is target species. It was determined that administering menbutone at a dose of 10 mg·kg^{-1} did not alter SOD, GPX, CAT, MDA, and 8–OHDG levels in sheep ($P>0.05$, TABLE I). Following menbuton administration, it is expected that the increased secretion of antioxidant bile acids and bilirubin will also exhibit antioxidant effects. Hence, menbuton may reduce oxidative status parameters, even indirectly. However, there is no literature on the effects of menbutone on oxidative stress parameters. Studies on the effects of drugs on oxidative stress parameters in sheep frequently examine serum levels of SOD, GPX, CAT, MDA, and 8–OHDG [13, 22, 23, 24].

It is stated that the SOD enzyme is responsible for converting two superoxide radicals into hydrogen peroxide by combining them with two hydrogen atoms. It is reported that the GPX and

CAT enzymes inactivate hydrogen peroxide by converting it into molecular oxygen and water [5]. MDA is formed as a result of lipid peroxidation and is accepted as a biomarker of oxidative stress [7].

Furthermore, 8–OHDG is frequently used in studies to identify damage to DNA caused by oxidative stress [9, 10]. Sheep are reported to have high antioxidant capacity [12]. When menbutone (10 mg·kg^{-1}) was administered to sheep, it can be stated that it will not cause oxidative stress and DNA damage and may be safe.

In the study, the effects of menbutone (10 mg·kg^{-1}) administered to sheep on serum heart, liver, and kidney function parameters were investigated. It was determined that menbutone had no adverse effects on serum troponin I, CK-MB isoenzyme, ALP, ALT, AST, BUN, and creatinine levels in sheep (P>0.05, TABLE II). Troponin I and CK-MBiso levels are accepted as markers of heart damage and are preferred in studies investigating the cardiotoxic effects of drugs in sheep [17, 18].

Hepatic enzymes can be divided into two groups: markers of hepatocellular damage and markers of cholestasis. Increased serum ALT or AST indicates hepatocellular damage, while ALP levels elevate in bile duct damage [20]. Circulating creatinine and BUN concentrations are the most used markers of kidney function [19, 25].

It was reported that administration of menbutone at a dose of 400 mg·kg^{-1} (IM) in rabbits resulted in increases in creatine kinase (CK), CK-MB, ALT, AST, and ALP levels. It was also stated that interstitial myocarditis and multifocal necrosis in the heart, necrosis with fatty infiltration in the liver, interstitial nephritis and renal tubular necrosis in the kidneys were determined [26]. Based on the findings of this research, it can be stated that menbutone at the recommended doses for sheep may not cause adverse effects on the heart, liver, and kidneys.

In the current research, the effect of menbutone on lipid metabolism parameters such as LDL and HDL levels in sheep was not determined (P>0.05); however, it caused statistically significant fluctuations in cholesterol levels (P<0.05) and a temporary increase in triglyceride level at 12th h (P<0.05) (TABLE II). However, these changes were not dramatically significant and are likely within the reference range.

No clinically adverse effects were observed in the study when menbutone was administered to sheep. It has been stated that intravenous treatment of menbutone may cause side effects such as increased salivation, lacrimation, respiratory distress, tremors, restlessness, and involuntary urination and defecation [3].

It has been reported that menbutone might cause myonecrosis in a horse after accidental intramuscular injection [27] and the administration of metoclopramide and menbutone to a cat caused intestinal invagination [28]. When menbutone (10 mg·kg^{-1}) was administered to Central Anatolian Merino sheep, it did not cause clinical side effects, and its use can be considered safe.

CONCLUSIONS AND IMPLICATIONS

This study investigated the effects of menbuton administration at the recommended dose and duration on serum oxidative stress markers, cardiac, hepatic, and renal function, and lipid profile parameters in sheep. According to the results of this study, it can be stated that menbutone has no effect on oxidative status parameters, does not affect heart, liver, and kidney functions, has a temporary minimal effect on lipid metabolism, and may be generally safe for sheep. However, studies are needed in target species with disease models.

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Conflict of interest

The authors declare that they have any conflict of interest.

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