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Research Article

The effect of oral administration of robenacoxib on hematological and biochemical parameters in different goat breeds

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ABSTRACT

Robenacoxib is a coxib-class, highly selective cyclooxygenase-2 inhibitor that is used to control pain and inflammation. This study aimed to determine the effect on hematological and biochemical parameters 24 hours after oral administration of robenacoxib to healthy Alpine and Saanen goats. The study was conducted on healthy females, 1-2 years old Alpine (n=5) and Saanen (n=5) goats. A single dose of robenacoxib was administered orally to goats at a dose of 4 mg/kg body weight. Blood samples were taken before (0 hour) and 24 hours after the administration of robenacoxib to evaluate of hematological and biochemical changes. The results of this study showed that statistical differences in hematological and biochemical parameters were within the normal limits in Alpine and Saanen goats except lactate dehydrogenase in Saanen goats. Furthermore, no differences were observed in hematological parameters between goat breeds; it can be claimed that the Alpine breed is more susceptible to negative pharmacological side effects than the Saanen breed according to changes in biochemical parameters. As a result, it was concluded that robenacoxib did not have a negative effect on kidney and liver functions and blood components in Alpine and Saanen goats in the administered dose and treatment period in this study. Further studies need to investigate the effects of robenacoxib in high doses, long-term use, and in disease conditions, especially on the kidney.

INTRODUCTION

Changes in moral and ethical considerations have led to global demands for better welfare conditions for food animals and the need for better agricultural practices. From this perspective, controlling pain sensation is one of the critical parameters necessary for improving livestock welfare. In addition to improving animal welfare standards, analgesia is also necessary both to facilitate procedures and to improve animal and personnel safety (Smith et al., 2021).

Goats are very pain-sensitive animals and cannot tolerate pain-inducing procedures. In the postoperative period, sudden deaths have been reported in goats, which have been attributed to catecholamine-induced ventricular fibrillation resulting from inadequate analgesia (Gray and McDonell, 1986). Chronic pain without relief produces significant stress and changes in behavior, as well as cardiopulmonary, neuroendocrine, metabolic, immunological, and thermoregulatory disorders (Anderson and Muir, 2005).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in veterinary and human medicine due to their anti-inflammatory, analgesic, and antipyretic effects. NSAIDs act by inhibiting various cyclooxygenase (COX) enzyme isoforms that play a role in the synthesis of prostaglandins, which have important efficacy in inflammatory and physiological events (Gunaydin and Sirri Bilge, 2018). Non-inducible COX-1, which is expressed by many body tissues, stimulates prostaglandin production for beneficial effects in the gastrointestinal tract, kidneys, nervous, reproductive, and cardiovascular systems (Clark, 2006). On the other hand, COX-2 is induced locally and for a limited time and is mainly responsible for inflammation and pain (Morita et al., 1995). Therefore, NSAIDs with a broad therapeutic index (selective COX-2 inhibitors, COXIBs) have been developed (Flower, 2003). Robenacoxib, one of the COXIBs that selectively inhibit COX-2, has been marketed as injectable and tablet formulations for cats and dogs (EMA, 2008). Animal species other than cats and dogs could potentially benefit from this drug.

There are no NSAIDs approved for use in the treatment of pain in small ruminants in Türkiye, USA, and Europe (Smith et al., 2021; Traş et al., 2021). As a result, these drugs are used off-label. Depending on the use of off-label drugs, treatment failure, drug-related adverse effects, a decrease in the production of healthy and quality animal product and economic losses may occur. Changes in hematological and biochemical parameters can be observed as a result of drug-related adverse effects (Amin et al., 2017; Owumi and Dim, 2019).

Hematological and biochemical parameters are considered indicators of structural toxic effects (Thrall, 2004). The effect of robenacoxib on hematological and biochemical parameters in goats has not been reported so far. In addition, studies have shown that there are differences among goat breeds concerning their hematological and biochemical profiles (Azab and Abde-Maksoud, 1999; Tibbo et al., 2004). Alpine and Saanen breeds generally have high adaptability and strong constitutions. One of the breeds' most important characteristiscs is their quick adaptation to different climatic conditions. Their

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feed utilization ability is high (Gall 1996). Because of these features, Alpine and Saanen goats were chosen in this study, which are raised almost all over the world. The purpose of this study is to investigate whether robenacoxib affects hematological and biochemical markers in different goat breeds (Alpine and Saanen) at 24 hours (24-h) after an oral single dose administration.

MATERIALS and METHODS

Animals

The study was carried out on a total of 10 goats of Alpine (n=5) and Saanen (n=5) breeds, 1-2 years old, 25-35 kg in weight, determined to be healthy by general clinical examination. The animals did not receive any other medications for at least 2 months prior to the beginning of this study. Goats according to breed, were kept in separate compartments from the other animals on the farm during the study. The goats were fed drug-free commercial feed twice a day and had free access to dried alfalfa grass and water. The experimental procedures in this study were approved by the Ethics Committee of the Cukurova University, Health Sciences Experimental Application and Research Center. This study was carried out at the Dairy Goat Research Farm, Faculty of Agriculture, Cukurova University, Adana, Türkiye.

Experimental Design

A single dose of robenacoxib (40 mg/tablet, Onsior®, Elanco) was administered orally at a dose of 4 mg/kg (Fadel et al., 2023) to goats. During the study, the animals were clinically observed. Before (0 hour, control) and at the 24-h after the administration, 3 mL of blood samples were taken with a vacutainer into tubes with K_3EDTA for hematological analyses and without anti-coagulant for biochemical analyses. Hemotological measurements were performed immediately after blood collection. The blood samples taken for biochemical measurement were centrifuged for 10 minutes (2500 ×*g*), and the serum samples obtained were stored at -20 °C until the analysis and analyzed within a week.

Analysis of Hematological and Biochemical Parameters

Measurement of hemotological parameters from blood samples taken into EDTA tubes (white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), neutrophils (Neu), lymphocytes (Lym), monocytes (Mon), eosinophils (Eos), basophils (Bas), neutrophils% (Neu%), lymphocytes% (Lym%), monocytes% (Mon%), eosinophils% (Eos%), and basophils% (Bas%)) were measured in a blood counter (Mindray BC-5000 Auto Hematology Analyzer, Mindray Bio-Medical Electronics, Shenzhen, China). Measurement of biochemical parameters (blood urea nitrogen (BUN), creatinine (CRE), total protein (TP), albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), lactate dehydrogenase (LDH), and creatine kinase (CK)) from serum samples was performed in an autoanalyzer device (Beckman Coulter AU 5800, Indianapolis, United States).

Statistical Analysis

Hematological and biochemical parameters were presented as mean ± SD. The SPSS program (23.0 software; IBM) was used for statistical analysis. The data obtained in the study were evaluated with the paired-t test. A value of $p < 0.05$ was accepted as the limit of statistical significance.

RESULTS

The current study investigated the effects of a single oral dose of robenacoxib on heamotological and biochemical parameters in Alpine and Saanen goat breeds. After oral administration of robenacoxib at a single dose of 4 mg/kg, no difference was detected in the feed and water consumption, rumination, defecation, urination, and movements of the goats during clinical observations. The findings indicated that a single oral dose of robenacoxib after 24-h treatment significantly altered some hematological and biochemical parameters within the reference range in both goat breeds (Table 1, Table 2, $p < 0.05$).

Alterations in Hematological Parameters

The effects of robenacoxib on hematological parameters in Alpine and Saanen goats were presented in Table 1. Robenacoxib showed no significant effect on WBC, HGB, MCV, Lym, Eos, Bas, Eos%, and Bas% after the 24-h treatment period when compared with the 0-h in the Alpine goat breed ($p < 0.05$; Table 1). While robenacoxib treatment significantly decreased RBC, HCT, Neu, and Neu%, MCH, Mon, Lym%, and Mon% were significantly increased after the 24-h treatment period when compared with the 0-h in Alpine goats ($p < 0.05$; Table 1). The obtained data revealed non-significant alteration in the WBC, HGB, Neu, Lym, Bas, Neu%, Eos%, and Bas% after the 24-h treatment period when compared with the 0-h in Saanen goats. However, robenacoxib had a significant effect on RBC, HCT, MCV, MCH, Mon, Eos, Lym%, and Mon% after the 24-h treatment period in this goat breed ($p < 0.05$; Table 1). The results indicated that there are significant decreases in RBC, HCT, MCV, and Lym% at 24-h treatment period in the Saanen goats ($p < 0.05$; Table 1). Additionally, MCH, Mon, Eos, and Mon% were significantly increased in the robenacoxib treated group at the 24-h treatment period in the Saanen goats when compared with the 0-h treatment period ($p < 0.05$; Table 1).

Alterations in Serum Biochemical Parameters

Robenacoxib effects on biochemical parameters in Alpine and Saanen goats were presented in Table 2. Robenacoxib had no significant effect on CRE, TP, Alb, and CK after the 24-h treatment period when compared with the 0-h in Alpine goats. The biochemical profiles, such as serum BUN levels and GGT enzyme activity were significantly increased, whereas serum AST, ALT, and LDH enzyme activities were significantly decreased at 24-h treatment period in Alpine goats ($p < 0.05$; Table 2). Robenacoxib significantly affected serum GGT and LDH activities after the 24-h treatment period when compared with the 0-h in the Saanen goats ($p < 0.05$; Table 2). Serum GGT and LDH activities were increased in robenacoxib treated Saanen goats at 24-h ($p < 0.05$; Table 2).

Table 1. Effects on hematological parameters (mean ± SD) after oral administration of a single dose of robenacoxib (4 mg/kg) to Alpine and Saanen goats (n=5)

Hematological Parameters	Alpine		Saanen		Reference Range
	0-h	24-h	0-h	24-h	
WBC (×10^9/L)	14.53±2.82	13.56±2.04	14.20±3.34	15.37±4.00	5.80-25.00
RBC (×10^{12}/L)	18.37±2.71	14.34±2.22*	15.53±0.72	14.46±0.81**	10.00-21.00
HGB (g/dL)	9.78±0.90	8.46±0.84	8.68±0.80	8.70±0.85	6.2-13.5
HCT (%)	24.66±1.64	19.22±1.46*	21.90±1.58	20.04±1.53**	19.00-36.00
MCV (fL)	13.58±1.40	13.54±1.34	14.08±0.62	13.84±0.53**	13.00-23.00
MCH (pg)	5.38±0.35	5.94±0.38*	5.58±0.33	6.02±0.36**	4.2-7.8
Neu (×10^9/L)	7.23±1.89	5.78±1.39*	6.41±2.51	6.95±2.20	2.12-10.10
Lym (×10^9/L)	6.86±1.18	7.05±1.36	7.37±1.32	7.59±2.32	3.12-22.10
Mon (×10^9/L)	0.08±0.03	0.32±0.14*	0.13±0.05	0.39±0.11**	0.00-1.42
Eos (×10^9/L)	0.31±0.27	0.36±0.12	0.21±0.09	0.34±0.08**	0.00-1.32
Bas (×10^9/L)	0.06±0.02	0.06±0.02	0.08±0.03	0.10±0.03	0.00-0.35
Neu %	49.18±7.21	42.4±8.23*	44.36±6.97	44.96±6.30	13.0-58.0
Lym %	47.92±7.52	52.22±8.78*	52.70±7.17	49.52±6.75**	35.0-83.0
Mon %	0.50±0.12	2.30±0.93*	0.86±0.11	2.58±0.72**	0.0-11.0
Eos %	2.00±1.47	2.64±0.69	1.56±0.64	2.28±0.66	0.0-8.0
Bas %	0.42±0.11	0.44±0.15	0.52±0.16	0.66±0.13	0.0-2.5

WBC: White blood cells, RBC: Red blood cells, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, Neu: Neutrophils, Lym: Lymphocytes, Mon: Monocytes, Eos: Eosinophils, Bas: Basophils, Neu%: Neutrophils%, Lym%: Lymphocytes%, Mon%: Monocytes%, Eos%: Eosinophils%, Bas%: Basophils%
*: The value determined at 24-h in Alpine goats is significantly different ($p<0.05$) from 0-h.
**: The value determined at 24-h in Saanen goats is significantly different ($p<0.05$) from 0-h.

Table 2. Effects on biochemical parameters (mean ± SD) after oral administration of a single dose of robenacoxib (4 mg/kg) to Alpine and Saanen goats (n=5)

Biochemical Parameters	Alpine		Saanen		Reference Range
	0-h	24-h	0-h	24-h	
BUN (mg/dL)	16.26±1.41	20.10±1.69*	15.52±2.40	18.88±3.84	10-28
CRE (mg/dL)	0.46±0.03	0.44±0.04	0.43±0.06	0.39±0.06	0.3-0.8
TP (g/L)	69.78±2.76	68.34±2.44	72.82±4.57	72.62±5.44	65-75
Alb (g/L)	31.23±1.42	31.52±1.54	31.37±1.84	30.58±1.69	27-45
AST (U/L)	92.60±8.35	82.00±9.27*	78.60±9.63	88.80±14.07	66-230
ALT (U/L)	26.20±2.59	21.60±2.07*	19.00±5.39	19.40±4.51	15-52
GGT (U/L)	42.00±6.52	44.80±7.05*	45.80±9.04	47.80±8.11**	20-56
LDH (U/L)	400.20±48.54	356.60±53.80*	361.20±33.70	413.00±62.93**	0-400
CK (U/L)	184.60±20.19	173.60±41.29	192.80±16.27	217.40±48.60	116-464

BUN: Blood urea nitrogen, CRE: Creatinine, TP: Total protein, Alb: Albumin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyltransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase
*: The value determined at 24-h in Alpine goats is significantly different ($p<0.05$) from 0-h.
**: The value determined at 24-h in Saanen goats is significantly different ($p<0.05$) from 0-h.

DISCUSSION

NSAIDs are the group most often used in human and veterinary medicine. The use of NSAIDs off-label in painful and inflammatory conditions raises concern about their safety in sheep and goats because there are no approved NSAIDs for these species. Studies evaluating hematological and biochemical parameters after administration of NSAIDs with greater COX-2 selectivity than COX-1 to farm animals are limited (Durna Çorum and Yıldız, 2020), and no studies investigating the effects of COXIBs on ruminants were found in the literature review. This is the first study to evaluate hemato-

logical and biochemical parameters after oral administration of robenacoxib in different goat breeds. This study's results demonstrated no significant effects on hematological parameters in Alpine and Saanen goats after a 4 mg/kg single oral dose of robenacoxib at 24-h treatment. Similarly, there were no significant alterations in biochemical parameters in Alpine goats except for a significant increase in LDH enzyme activity at 24-h in Saanen goats.

The gastrointestinal tract, kidney, liver, and inhibition of blood clotting are the main targets of NSAID toxicity (Warner et al., 1999; Flower, 2003). Robenacoxib acts by inhibiting COX-2 specifically, which is responsible for prostaglandin synthesis, which is an essential component of pain. The selective COX-2 NSAID displayed several adverse effects regarding the integrity of hepatocellular damage, renal impairment, and raising WBC, with varying effects on different leukocyte subtypes (Wright, 2002). No important changes were determined in the hematological parameters after 24-h robenacoxib treatment in both goat breeds in this study. Furthermore, observed changes in hematological parameters for robenacoxib-treated Alpine goats were determined within their normal range. The decreases in RBC, HCT, and increases in MCH and Mon in both Alpine and Saanen goats were within the reference values, and similar results were obtained from celecoxib-treated healthy adults (Leese et al., 2000). Tabrizi et al. (2006) reported that celecoxib did not have significant effects on hematological results including WBC, RBC, and platelet counts, as well as the levels of PCV, HGB, MCV, MCH, and MCHC in dogs. Similar to these findings, meloxicam and ketoprofen did not alter the hematological parameters of healthy ponies (Pozzobon et al., 2009). Villegas et al. (2002) reported that piroxicam and meloxicam did not significantly affect hematological parameters in rats.

Some enzymes, proteins, and nucleic acids in the blood associated with specific tissue damage can be used to detect most drug-related adverse effects and, in some cases, to determine the prognosis (Tang and Lu, 2010; Özdemir and Traş, 2018). Measured in living beings, CRE and BUN are used to define kidney damage, AST, ALT, Alb, GGT, LDH, and TP are used to define liver damage, and CK is used to define heart damage (Gowda et al., 2009; Kim and Moon, 2012). Recently, it was reported that there was no evidence of robenacoxib toxicity in the liver or kidneys of cats or dogs. According to this research, in cats and dogs treated with robenacoxib subcutaneously and orally, alkaline phosphatase, ALT, AST, GGT, CRE, and BUN were not affected when compared to baseline levels or controls (Toutain et al., 2017; Heit et al., 2020). Previously, the critical role of COX-2 in maintaining kidney function was demonstrated by Gertz et al. (2002) and Whelton et al. (2000). Therefore, the adverse renal effects of COXIBs may be similar to those of non-selective COX inhibitors. In cases of acute kidney injury caused by NSAIDs, serum CRE and BUN values increase (Harris, 2006). There was no difference in serum CRE level between 0-h and 24-h in both goat breeds, while a statistically significant increased BUN value was found in Alpine goats at 24-h compared to 0-h within the reference range in the current study. Furthermore, lower values for AST and ALT can be detected in renal failure cases compared to the normal population (Ersoy, 2012). Similar to this finding, AST and ALT enzyme activities statistically decreased at 24-h after robenacoxib administration in Alpine goats compared to 0-h in the present study. The possible relevance of elevated serum GGT activity with the development of chronic kidney disease is known, but the literature on this subject is controversial and very limited in number (Noborisaka et al., 2013). In this study, a statistically increase in GGT activity at 24-h compared to 0-h was detected in both Alpine and Saanen goats. Firocoxib, one of the coxibs, had been administered orally at a dose of 5 mg/kg to healthy dogs, an increase in GGT activity had been determined within the reference range, but the researchers did not find it related to firocoxib (Steagall et al., 2007). In Saanen goats, an increase in LDH level over the reference range was observed at the 24-h. Laboratory abnormalities such as increased LDH is apparent in thrombotic microangiopathy. Thrombotic microangiopathy associated with pharmaceutical agents is usually caused by disorders of the hemolytic uremic syndrome (Shirali and Perazella, 2015). Low LDH is a rare condition and in this study, the decrease in LDH at 24-h in Alpine goats could not be related to robenacoxib treatment in the current study.

In this study, it was determined that robenacoxib administered orally at a dose of 4 mg/kg to different goat breeds did not cause any change in hematological and biochemical parameters except LDH enzyme activity in Saanen goats. These results show that oral robenacoxib administration does not cause any pathological changes in hematological and serum biochemical parameters in goats and appears to have been well tolerated by goats.

CONCLUSION

The results obtained from this study are the first data that the effects of oral administered robenacoxib on hematological and serum biochemical parameters in Alpine and Saanen goats. It was showed that statistical differences of hematological and biochemical parameters were within the normal limits in Alpine and Saanen goats except for LDH enzyme activity in Saanen goats. Moreover, while no differences were observed in hematological parameters according to goat breeds, when biochemical parameters are evaluated, it can be said that Alpine breed is exposed to adverse drug effects compared to Saanen breed. Administration of robenacoxib did not cause any adverse effects on hematological parameters or serum biochemisty in both goat breeds and it was suggested that it may be used as an alternative to existing NSAIDs. Furthermore, there is a need to investigate the effects of robenacoxib in high doses, long-term use, and disease conditions, especially on the kidney.

DECLARATIONS

Ethics Approval

All protocols in animals were approved by the Ethics Committee of the Cukurova University, Health Sciences Experimental Application and Research Center.

Conflict of Interest

The authors declare that they have no known competing fi-

nancial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent for Publication

Not applicable.

Author contribution

Idea, concept and design: ZOK

Data collection and analysis: ZOK, PPB

Drafting of the manuscript: ZOK, PPB

Critical review: ZOK

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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