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RESEARCH ARTICLE

Hematological and biochemical effect of subcutaneous administration of robenacoxib in different goat breeds

Zeynep Ozdemir Kutahya*, Petek Piner Benli

Cukurova University, Faculty of Ceyhan Veterinary Medicine, Department of Veterinary Pharmacology and Toxicology, Adana, Türkiye

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*zkutahya@cu.edu.tr

Robenacoxibin farklı keçi ırklarına deri altı yolla uygulanmasının hematolojik ve biyokimyasal etkisi

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Öz

Amaç: Sunulan çalışmada sağlıklı Alpin ve Saanen ırkı keçilere robenacoxibin deri altı yolla uygulamasından 24 saat sonra hematolojik ve biyokimyasal parametreler üzerindeki etkisinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Çalışmada 12 Alpin (n=6) ve Saanen (n=6) ırkı, sağlıklı keçi kullanıldı. Alpin ve Saanen ırkı keçilere robenacoxib 4 mg/kg dozda, tek sefer deri altı yolla uygulandı. İlaç uygulamasından önce (0. saat) ve 24. saatte kan örnekleri toplandı. Hematolojik ve biyokimyasal parametreler hematoloji analizörü ve biyokimya otoanalizörü cihazları kullanılarak analiz edildi.

Bulgular: Her iki keçi ırkının klinik muayene bulgularında değişiklik gözlenmedi. Hematolojik ve biyokimyasal parametrelerdeki istatistiksel farklılıklar her iki keçi ırkında fizyolojik sınırlar içerisinde belirlendi. Alpin ırkı keçilerde beyaz kan hücresi, kırmızı kan hücresi, lenfosit değeri düşük ve % monosit değeri yüksek belirlendi. Saanen ırkı keçilerde kırmızı kan hücresi, hemoglobin ve hematokrit değerlerinin düşük, ortalama korpüsküler hacim ve ortalama korpüsküler hemoglobin değerlerinin ise 24 saatte yüksek olduğu gözlemlendi. Robenacoxib her iki keçi ırkında da kan üre nitrojen değerini arttırırken, Saanen keçilerinde kreatinin değerini düşürdü.

Öneri: Robenacoxibin Alpin ve Saanen ırkı keçilere uygulanmasından sonra hematolojik ve biyokimyasal parametrelerde önemli bir değişiklik belirlenmedi. Sonuç olarak, yüksek doz ve tekrarlanan uygulamalarda, karaciğer ve böbrek fonksiyon bozukluklarında, yaş, ırk, farklı fizyolojik durumlarda robenacoxibin etkilerinin araştırılacağı çalışmalara ihtiyaç vardır. Kan profilinde herhangi bir olumsuz etki görülmemesi nedeniyle robenacoxibin keçilerde ağrı ve inflamasyonun önlenmesinde alternatif bir NSAID olarak kullanılabileceği değerlendirildi.

Anahtar kelimeler: Biyokimyasal, deri altı, hematolojik, keçi ırkı, robenacoxib

Abstract

Aim: This study aimed to investigate the effect of robenacoxib on hematological and biochemical parameters in healthy Alpine and Saanen goats 24 hours after subcutaneous administration.

Materials and Methods: 12 healthy Alpine (n=6) and Saanen (n=6) breed goats were used. Robenacoxib was administered to Alpine and Saanen goats at a dose of 4 mg/kg once subcutaneously. Blood samples were collected before drug administration (0 hour) and then 24-hours. Hematological and biochemical parameters were analyzed using a hematology analyzer and biochemistry auto analyzer, respectively.

Results: No change was observed in the clinical examination findings of both goat breeds. Statistical differences in hematological and biochemical parameters were determined within physiological limits in both goat breeds. The white blood cell, red blood cell and lymphocyte values were found to be low, and the monocyte% value was found to be high in Alpine goats. Decreases in red blood cell, hemoglobin and hematocrit levels and increases in the mean corpuscular volume and mean corpuscular hemoglobin values were observed at 24-hours in Saanen goats. Robenacoxib increases blood urea nitrogen value in both goat breeds, it decreases creatinine value in Saanen goats.

Conclusion: There were no significant changes in hematological and biochemical parameters after robenacoxib administrations to Alpine and Saanen goats. Consequently, further studies are needed to investigate the effects of robenacoxib in high-dose and repeated administrations, liver and kidney dysfunctions, different age, breed, and physiological conditions. It was evaluated that robenacoxib could be used as an alternative NSAID to prevent pain and inflammation in goats, since no adverse effect was observed in the blood profile.

Keywords: Biochemical, goat breed, hematological, robenacoxib, subcutaneous

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Introduction

Robenacoxib (RX) is a new nonsteroidal anti-inflammatory drug (NSAID) of the coxib family with anti-hyperalgesic, anti-inflammatory, and antipyretic properties (Lees et al 2022). RX is a diclofenac structural analogue (Schmid et al 2010). Coxibs inhibit the cyclooxygenase-2 (COX-2) isoform of the cyclooxygenase (COX) enzyme preferentially (Cairns 2007). The two COX isoforms, cyclooxygenase-1 (COX-1) and COX-2, are almost identical in structure but have significant differences in substrate and inhibitor selectivity. COX-1 is constitutively found in numerous tissues and possesses multiple protective roles, such as gastric cytoprotection, renal blood flow regulation, and platelet activity regulation, whereas COX-2 is mainly produced locally and for short periods and is responsible for pain and inflammation (Pairet and Engelhardt 1996). COX-2-selective drugs have been produced, which allow for stronger suppression of COX-2, the inducible COX isoform linked with inflammation (Vane and Botting 1995). RX is a selective COX-2 inhibitor; injectable and tablet formulations are approved for cats and dogs (Lees et al 2022). RX is strongly bound to plasma proteins (>98%) in both cat and dog plasma (Jung et al 2009). Researchers found that systemically available RX was excreted in both cats and dogs through feces and urine; however, feces accounted for the majority of excretion (64.6% in dogs and 72.5% in cats) and was thought to be the result of biliary excretion (King and Jung 2021).

Goats, which have been used for thousands of years for their milk, meat, hair, and skin, have seen an important increase in popularity in the past few decades. The market shares for goat milk and products made from goat milk are rapidly expanding in many nations throughout the world, particularly in industrialized countries (Boyazoglu et al 2005). The growing interest in goats as farm animals and domestic animals in recent years has highlighted the need to improve and prolong goat life quality. Farm animal welfare and pain treatment have lately been popular study subjects among the researchers (Grandin 2014, Shivley et al 2016). Chronic pain in farm animals has been shown to reduce food consumption, raise blood pressure, and lower body temperature (Stewart et al 2010). Adequate analgesia is required to reduce physiologic stress, improve animal welfare and convalescence, and increase the efficacy of treatment (Baller and Hendrickson 2002; Gleerup and Lindegaard 2016). Acute and chronic pain conditions in small ruminants include disbudding and castration, osteoarthritis, fracture, spondylitis, foot rot and abscess, corneal ulceration, and the postoperative period (Anderson and Muir 2005, Galatos 2011, Plummer and Schleining 2013, Karademir et al 2016).

There are no approved drugs in Türkiye, Europe, or the United States for pain management in small ruminants (Lizarraga and Chambers 2012, Smith et al 2021, Traş et al 2021). For this reason, many drugs are used off-label for pain management in goats and other small ruminants. Generally, indications for use and dosage regimens of NSAIDs in small ruminants are adjusted according to the cattle label (Reppert et al 2019), which can cause drug-related adverse effects and economic losses.

Many of the drugs cause adverse effects of varying severity and nature, as well as therapeutic effects (Coleman and Pontefract 2016). Generally, biochemical and hematological changes are indicate of structural toxic effects (Traş et al 1999, Balamuthusamy and Arora 2007). Studies have shown differences in hematological and biochemical profiles between goat breeds (Azab and Abde-Maksoud 1999, Tibbo et al 2004). There is no data related to effects of RX after subcutaneous administration on hematological and biochemical parameters in different goat breeds. As a continuation of our previous study, the present study aimed to investigate the changes in hematological and biochemical parameters 24-hours (24-h) after subcutaneous administration of a single dose of RX (4 mg/kg) in Alpine and Saanen goats.

Material and Methods

Animals

The research was conducted on 12 healthy goats of the Alpine (n=6) and Saanen (n=6) breeds, female, 1-2 years old. The animals were evaluated as healthy by general clinical examination and were not given any medication for 2 months before the study. The goats were kept in separate pens according to breed during the study. Drug-free feed was provided *ad libitum* twice daily. Animals were allowed free access to alfalfa hay and water.

Experimental design

RX (Onsior®, 20 mg/mL, Elanco) was administered once subcutaneously at a dose of 4 mg/kg (Fadel et al 2023) into the axillary region of each goat. Goats were observed throughout the study for water intake, defecation, urination, rumination, local tissue reactions such as swelling and rash. Blood samples were taken from the jugular vein through jugular venipuncture before (0-h) and 24 hours after drug administration into gel-containing tubes for biochemical analyses (3 mL) and EDTA-containing tubes for hematological studies (3 mL). Measurement of hematological parameters was carried out shortly after taking blood samples. Blood samples were centrifuged at 2500 *g* for 10 minutes for biochemical parameters measurement, and the separated serum was kept at 20°C until analysis, which was completed within one week.

Hematological and biochemical analyzes

Hematological parameters including 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 determined by hematology analyzer (Mindray BC-5000 Auto Hematology Analyzer, Mindray Bio-Medical Electronics, Shenzhen, China). Biochemical parameters including blood urea nitrogen (BUN), creatinine (CRE), total protein (TP), albumin (Alb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), and creatine kinase (CK) were analyzed by serum biochemistry auto analyzer (Beckman Coulter AU 5800, Indianapolis, United States).

Statistical analysis

Data were statistically analyzed using SPSS software version 23.0 (IBM SPSS Statistics, NY, USA). The Wilcoxon Signed Ranks tests were conducted for analyzing biochemical and hematological data at significance level $P < 0.05$. The results were expressed as mean±SD.

Results

No local or systemic adverse effects were observed in goats after subcutaneous administration of RX at a dose of 4 mg/kg. A significant difference at $P < 0.05$ was found in the WBC, RBC, Lym and Mon% value in the Alpine goats and levels of RBC, HGB, HCT, MCV, and MCH in the Saanen goats at the 24-h treatment period when compared to the 0-h. Although RX treatment caused significant decreases in WBC, RBC and Lym values, and increase in Mon% in Alpine goats, it caused significant decreases in RBC, HGB, and HCT values and increases in values of MCV and MCH in the Saanen goats at 24-h (Table 1).

The serum biochemical profiles of RX-treated Alpine and Saanen goats are shown in Table 2. No statistically significant differences were detected in CRE, TP, and Alb levels, as well as AST, ALT, GGT, and CK activities, in the Alpine goats at the 24-h treatment period when compared to the 0-h treatment period ($P < 0.05$). There was a statistically significant increase in BUN levels in the RX-treated Alpine goats at 24-h when compared to the 0-h treatment period. There was no statistically significant difference at $P < 0.05$ for TP and Alb levels or AST, ALT, GGT, and CK activities in the Saanen goats at 24-h compared to the 0-h. BUN levels were found higher and CRE levels were found lower in RX-treated Saanen goats at 24-h when compared to the 0-h treatment period.

Discussion

NSAIDs are among the most used drug groups after antibiotics in the veterinary field, but there is no approved NSAID for use in goats. Therefore, NSAIDs are used off-label in goats, and not knowing the safety of the NSAIDs used may create a risk to both animal and human health. Long-term and high-dose use of NSAIDs has significant side effects on the gastric mucosa, cardiovascular system, and blood profile and causes alterations in renal function (Bennett et al 1996, MacDonald et al 1997, Huntjens et al 2005, Higuchi et al 2009). NSAIDs can cause delays in healing gastric ulcers, hemorrhages, perforations, and ulcers in the gastrointestinal system (MacDonald et al 1997). Furthermore, they have been shown to have side effects on the cardiovascular system, such as inhibition of platelet aggregation, disturbance of electrolyte balance in the kidneys, and associated hypertension. NSAIDs, especially COX-2 inhibitors, can also cause myocardial infarction and heart attack (Huntjens et al 2005). The current study showed how administration of subcutaneous RX at a dose of 4 mg/kg in goats of the Alpine and Saanen breeds alters the blood profile (hematological and biochemistry). The research results demonstrated that statistical changes in hematological and biochemical parameters after subcutaneous administration of RX to two different goat breeds were within the physiological range.

To evaluate drugs' impact on physiological and pathological conditions, hematological and biochemical indicators are used. NSAIDs are a class of drugs that are known to affect the hematopoietic system in animal models (Hofer et al 2012) and blood profiles in farm animals (Turgut et al 2018, Yıldız et al 2018, Yipel and Güngor 2021). Biochemical changes in animal species are generally accepted as messengers of pathological side effects (Riviere and Papich 2018). While hematological parameters such as HGB, RBC, WBC and HCT provide information about fluid-electrolyte balance and bone marrow functions, biochemical parameters such as BUN, CRE, TP, Alb, AST, ALT, GGT, and CK give information about kidney, liver, heart, and general health status (Washington and Van Hoosier 2012). In this study, statistical decreases were observed at 24-h for WBC, RBC, and Lym values in Alpine goats and RBC, HGB, and HCT values in Saanen goats after subcutaneous administration of 4 mg/kg RX. Additionally, these changes were within the reference range for goats. Studies conducted in rats and monkeys demonstrated that a significant decrease in RBC, HGB and HCT values was determined after tepoxalin (Knight et al 1996), acetaminophen (Mokhtari et al 2023), diclofenac (Aycan et al 2018), meloxicam (Yipel and Güngor 2021), and lornoxicam (Atzpodien et al 1997). Aycan et al. (2018) reported that the decreases in RBC, HGB and HCT values may indicate bone marrow toxicity and gastrointestinal bleeding. Because of the RX is a structural analogue of diclofenac (Schmid et al 2010), similar adverse effects may occur in

Table 1. Effects on hematological parameters (mean±SD) after subcutaneous administration of a single dose of robenacoxib (4 mg/kg) to Alpine and Saanen goats (n=6)

Hematological Parameters	Alpine 0-h	Alpine 24-h	P value	Saanen 0-h	Saanen 24-h	P value	Reference Range
WBC (×10⁹/L)	17.08±1.93	14.52±3.58	0.028 ¥	18.43±5.06	16.50±3.81	0.116	5.80-25.00
RBC (×10¹²/L)	17.45±2.57	16.07±2.01	0.043 ¥	17.08±1.29	15.16±0.77	0.028 *	10.00-21.00
HGB (g/dL)	9.68±0.63	10.13±3.06	0.345	9.67±1.05	8.69±0.79	0.028 *	6.2-13.5
HCT (%)	24.21±0.99	24.80±5.91	0.344	23.82±1.88	21.58±1.33	0.028 *	19.00-36.00
MCV (fL)	13.85±1.38	13.77±1.48	0.785	13.95±0.48	14.23±0.52	0.027 *	13.00-23.00
MCH (pg)	5.52±0.37	5.55±0.34	0.317	5.65±0.28	5.72±0.32	0.046 *	4.2-7.8
Neu (×10⁹/L)	8.10±1.90	7.06±2.83	0.116	9.16±4.12	7.27±2.62	0.116	2.12-10.10
Lym (×10⁹/L)	8.60±1.39	7.12±1.96	0.028 ¥	8.88±1.79	8.88±2.06	0.463	3.12-22.10
Mon (×10⁹/L)	0.06±0.04	0.08±0.04	0.078	0.095±0.04	0.095±0.04	1.000	0.00-1.42
Eos (×10⁹/L)	0.27±0.17	0.21±0.16	0.058	0.21±0.13	0.17±0.08	0.172	0.00-1.32
Bas (×10⁹/L)	0.06±0.01	0.05±0.03	0.715	0.09±0.03	0.08±0.02	0.257	0.00-0.35
Neu %	47.20±8.10	47.79±10.90	0.833	48.47±8.40	43.61±9.13	0.116	13.0-58.0
Lym %	50.60±8.43	50.03±11.39	0.917	49.53±8.81	54.38±9.32	0.116	35.0-83.0
Mon %	0.33±0.18	0.55±0.18	0.026 ¥	0.48±0.09	0.53±0.20	0.334	0.0-11.0
Eos %	1.55±0.92	1.30±0.80	0.207	1.07±0.45	1.02±0.35	0.340	0.0-8.0
Bas %	0.32±0.08	0.33±0.12	0.783	0.45±0.15	0.45±0.15	1.000	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%

Table 2. Effects on biochemical parameters (mean±SD) after subcutaneous administration of a single dose of robenacoxib (4 mg/kg) to Alpine and Saanen goats (n=6)

Biochemical Parameters	Alpine 0-h	Alpine 24-h	P value	Saanen 0-h	Saanen 24-h	P value	Reference Range
BUN (mg/dL)	19.72±2.10	22.43±1.94	0.028 ¥	16.22±1.99	19.65±3.02	0.027 *	10-28
CRE (mg/dL)	0.53±0.05	0.48±0.06	0.073	0.51±0.06	0.45±0.06	0.026 *	0.3-0.8
TP (g/L)	72.08±2.06	70.25±2.81	0.080	76.38±3.08	74.40±4.85	0.173	62-79
Alb (g/L)	32.92±1.91	32.25±1.39	0.116	32.06±1.90	31.28±1.79	0.173	27-45
AST (U/L)	88.33±10.88	100.33±32.32	0.279	82.67±16.37	85.17±16.03	0.673	66-230
ALT (U/L)	23.67±2.07	24.33±4.46	0.705	18.33±5.09	18.17±4.70	0.713	15-52
GGT (U/L)	44.50±6.72	46.17±8.06	0.206	51.67±12.55	51.50±11.78	0.785	20-56
CK (U/L)	259.33±180.44	189.83±34.70	0.833	271.50±98.65	247.50±100.41	0.674	116-464

BUN: Blood urea nitrogen, CRE: Creatinine, TP: Total protein, Alb: Albumin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyltransferase, CK: Creatine kinase
¥: The value determined at 24-h in Alpine goats is significantly different (P<0.05) from 0-h based on Wilcoxon Signed Ranks test.
*: The value determined at 24-h in Saanen goats is significantly different (P<0.05) from 0-h based on Wilcoxon Signed Ranks test.

high doses and long-term use of RX. There is not enough data to interpret changes in parameters analyzed in the present study including WBC, Lym, MCV, MCH and Mon% in researches conducted with COX-2 selective NSAID drugs such as RX.

Non-selective NSAIDs mainly inhibit COX-1, leading to adverse effects such as hepatotoxicity, inhibition of platelet function, and inhibition of prostaglandin formation necessary for normal gastrointestinal and renal function, especially when used for a long time (Bergh and Busberg 2005). Coxibs have been developed to reduce pain and inflammation in order to eliminate these adverse effects. However, studies have revealed that COX-2 inhibitors such as celecoxib, rofecoxib may cause adverse effects on the kidneys similar to non-selective NSAIDs (Perazella and Eras 2000, Perazella and Tray 2001, Morales and Mucksavage 2002). The most common renal complications of NSAIDs are increased BUN and CRE levels (Ejaz et al 2004, Harris 2006). In this study, the BUN value was determined to be statistically higher after subcutaneous administration of RX at 24-h in both Alpine and Saanen goats. Although the serum CRE value in Saanen goats was lower at 24-h, RX did not alter the CRE value in Alpine goats. Diclofenac, one of the classical NSAIDs that strongly inhibits the COX-2 enzyme, increased BUN and serum CRE in studies of rats (Besen et al 2009, Aycan et al 2018). Carprofen, which has more COX-2 selectivity than COX-1, was administered to sheep at different doses (4 mg/kg and 16 mg/kg), no change was observed in the CRE value, while the BUN value was higher in both administered doses (Durna Çorum and Yıldız 2020). Similar results were reported for other selective COX-2 inhibitors, such as meloxicam in different species including lamb, sheep, cat, and rat (Pehlivan et al 2010, Yipel and Güngor 2021, Kongara et al 2023, Wun et al 2023).

It was reported that significant changes in the pharmacokinetics of NSAIDs in between general exist between species and their effects depend on the species, associations with other drugs, and pharmacokinetics of the specific NSAID used (Welsh et al 1993, Cunningham and Lees 1994, Lees et al 1998) However, there are no comparative studies on the pharmacokinetics, hematological and biochemical effects of NSAIDs in different goat breeds. It was suggested that difference in the effect of RX on hematological and biochemical parameters between both breeds of goats could be related to presence of the metabolic differences between two breeds.

Conclusion

Overall, RX administered subcutaneously at a dose of 4 mg/kg in Alpine and Saanen goats did not cause a significant change in hematological and biochemical parameters.

Alpine goats may tolerate RX better than Saanen goats due to the fact that RX subcutaneous administration affects the hematological parameters more in the Saanen breed than the Alpine breed. The increase in BUN value within physiological limits in both goat breeds may indicate the adverse effects of selective COX-2 inhibitors on the kidney. More comprehensive studies are needed to investigate its possible effects on the hematopoietic, renal, and cardiovascular systems in high doses and repeated administrations under different physiological conditions such as liver and kidney dysfunction, age, and breeds. In the light of the aforementioned results, RX may be used as an alternative to reduce pain and inflammation since it does not adversely affect the blood profile by subcutaneous administration in Alpine and Saanen goats.

Conflict of Interest

The authors did not report any conflict of interest or financial support.

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Author Contributions

Concept: ZOK; Design: ZOK; Control: ZOK, PPB; Data Collection: ZOK; Analysis: ZOK, PPB; Literature Review: ZOK, PPB; Writing the Article: ZOK, PPB; Critical Review: ZOK.

Ethical Approval

All protocols in animals were approved (approval code: 23, approval date: 20.07.2023) by the Ethics Committee of the Cukurova University, Health Sciences Experimental Application and Research Center.