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The effect of cefquinome on hematological and biochemical parameters following repeated subcutaneous administrations in sheep

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Abstract: The objective of this study was to evaluate the effect of cefquinome on hematological and biochemical parameters following repeated subcutaneous administrations in sheep. The study was conducted with six clinically healthy Merino sheep with age and body weight of 1.5 ± 0.2 years and 39 ± 2.7 kg, respectively. Cefquinome was administered subcutaneously to the sheep once a day for five days at a dose of 2.5 mg/kg. Blood samples were collected by jugular venipuncture prior to drug administration (0 h) and at 48 h and 120 h following the first drug administration. Blood samples were analyzed to determine hematological and biochemical parameters. Hematological and biochemical parameters did not alter following repeated subcutaneous administration of cefquinome ($P > 0.05$). These results indicate that cefquinome could be safe and well-tolerated following repeated subcutaneous administrations of 2.5 mg/kg once daily for five consecutive days in sheep. However, there is a need for molecular and histopathological investigation of the safety of cefquinome after repeated administration in sheep at different doses and administration routes.
Keywords: Biochemistry, cefquinome, hematology, sheep

Koyunlarda tekrarlanan subkutan uygulamaları takiben sefkuinomun hematolojik ve biyokimyasal parametrelere etkisi

Özet: Bu çalışmanın amacı, koyunlarda tekrarlanan subkutan uygulamaları takiben sefkuinomun hematolojik ve biyokimyasal parametreler üzerindeki etkisini değerlendirmektir. Çalışma klinik olarak sağlıklı, 1,5 ± 0,2 yaş ve 39 ± 2,7 kg canlı ağırlığa sahip, altı adet Merinos koyunu üzerinde gerçekleştirildi. Sefkuinom koyunlara 2,5 mg/kg dozda günde bir defa beş gün boyunca deri altı yolla uygulandı. Kan örnekleri ilaç uygulaması öncesi (0. saat) ve ilk uygulamayı takiben 48. ve 120. saatlerde jugular venapunktur yöntemi ile toplandı. Kan örnekleri hematolojik ve biyokimyasal parametreleri belirlemek için analiz edildi. Sefkuinomun tekrarlanan subkutan uygulaması hematolojik ve biyokimyasal parametrelerde herhangi bir değişikliğe neden olmadı ($P > 0,05$). Bu sonuçlar, koyunlarda 2,5 mg/kg dozda sefkuinomun günde bir defa beş gün boyunca tekrarlanan subkutan uygulamasının güvenli ve iyi tolere edilebileceğini gösterdi. Ancak, koyunlarda farklı dozlarda ve uygulama yollarında tekrarlanan uygulamadan sonra sefkuinomun güvenilirliğinin moleküler ve histopatolojik olarak araştırılmasına ihtiyaç vardır.
Anahtar kelimeler: Biyokimya, sefkuinom, hematoloji, koyun.

Introduction

Cefquinome is a fourth-generation cephalosporin antibiotic developed exclusively for use in animals (CVMP, 2003). Cefquinome has a broad spectrum of antibacterial activity, including gram-negative and gram-positive bacteria, and it is considered to be highly stable against β-lactamases encoded by chromosomes and genes on plasmids (Durckheimer et al., 1988; Limbert et al., 1991). The main difference between cefquinome and previous generations is that it has a zwitterionic molecular structure, which increases its ability to penetrate the periplasmic space of the bacterium and improves resistance to β-lactamases (Limbert et al., 1991). In addition, cefquinome has favorable pharmacokinetic properties such as good absorption, high bioavailability, and primary elimination via the kidney (Corum et al., 2019). It has been approved for the treatment of acute mastitis and foot rot in cattle, respiratory tract diseases in cattle, pigs, and horses, calf and foal septicemia, and metritis-mastitis-agalactia syndrome in sows (CVMP, 1995; 1999; 2003).

Due to its broad antibacterial spectrum and excellent efficacy, cefquinome is used as an extra label in sheep for purposes indicated in other species. For the effective and safe use of drugs, the undesirable effects of extra-label use should be evaluated. Hematological and biochemical parameters may be useful in evaluating the adverse effects of drugs. Hematological parameters are used to evaluate bone-marrow functions and biochemical parameters are used to evaluate the functions of organs such as the liver and kidney (Corum et al., 2015; Corum et al., 2016; Durna Corum et al., 2020). Although the effect of cefquinome on hematological and biochemical parameters after repeated (2 mg/kg, every 24 h for 5 days) IM administration in sheep was revealed, no information was found after repeated SC administration. The aim of this study is to determine the effect of repeated (every 24 h for 5 days) subcutaneous administration of cefquinome at a dose of 2.5 mg/kg on hematological and biochemical parameters in sheep.

Material and Methods

***Animals*:** Six healthy female Merinos sheep, aged 1.5 ± 0.2 years and weighing 39 ± 2.7 kg, were used. The animals were judged as healthy by a physical examination, and they had not received any drug during the 4 weeks prior to the study. The sheep were kept in individual pens for 2 weeks before the study for the acclimation period. The sheep were fed with drug-free commercial feed twice a day, and alfalfa hay and water were given ad libitum.

***Experimental design*:** Cefquinome (Cobactan 2.5%, Intervet, İstanbul/Turkiye) was administered subcutaneously at a dose of 2.5 mg/kg into the axillary region of each sheep once daily for five consecutive days. Blood samples were collected into gel-containing tubes

for biochemical analyses (2 mL) and into EDTA-containing tubes for hematological analyses (2 mL) from the jugular vein through jugular venipuncture prior to drug administration (0 h) and at 48 h and 120 h following the first drug administration. For the analysis of biochemical parameters, blood samples were centrifuged at 4000 g for 10 min, and the separated serum was stored at −80°C until analysis. Additionally, sheep were observed clinically during the study.

***Hematological and biochemical analyzes*:** Hematological parameters such as white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, and platelet were measured by hemocell counter (Shenzhen Mindray Bio-Medical Electronics, BC-2800 Auto Hematology Analyzer, China). Biochemical parameters such as albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), cholesterol, creatine kinase (CK), creatinine, gamma-glutamyltransferase (GGT), total protein (TP), and triglyceride were analyzed by autoanalyzer (ILab-300 bioMerieux Diagnostics, Milan, Italy).

***Statistical analysis*:** All values were presented as mean ± SD. The normality of the data distribution was assessed with the *Shapiro-Wilk* test and the homogeneity of variance with *Levene's* test. Hematological and biochemical results were analyzed using a one-way analysis of variance and post hoc *Tukey* tests. SPSS 22.0 (IBM Corp, Armonk, NY) statistics program was used for the statistical analysis. $P < 0.05$ value was considered statistically significant.

Results

No local (lameness, redness, and pain at the injection site) or systemic (feed and water consumption, fecal production, and behavior) adverse effects were observed in any sheep after repeated administration of cefquinome. Hematological and biochemical parameters in sheep after repeated subcutaneous administration of cefquinome (2.5 mg/kg, every 24 h for 5 days) are presented in Table 1 and Table 2, respectively. Hematological (WBC, RBC, hemoglobin, hematocrit, and platelet) and biochemical (albumin, ALP, ALT, AST, BUN, cholesterol, CK, creatinine, GGT, TP, and triglyceride) parameters did not alter following repeated subcutaneous administration of cefquinome ($P > 0.05$).

Table 1: Effect of cefquinome (2.5 mg/kg, subcutaneous, every 24 h for 5 days) in sheep on hematological parameters (n = 6, mean ± SD)

Parameters	0 h	48 h	120 h
WBC ($^{x}10^{9}$/L)	7.67 ± 1.16	7.17 ± 1.13	6.97 ± 0.67
RBC ($^{x}10^{12}$/L)	12.73 ± 0.65	12.00 ± 1.31	11.95 ± 1.25
Hemoglobin (g/dL)	11.83 ± 1.01	10.95 ± 0.85	11.48 ± 1.04
HCT (%)	34.57 ± 2.17	32.02 ± 3.05	31.35 ± 2.78
Platelet ($^{x}10^{9}$/L)	301.33 ± 76.66	304.17 ± 72.46	269.17±55.95

WBC; white blood cells, RBC; red blood cells, HCT; hematocrit.

Table 2: Effect of cefquinome (2.5 mg/kg, subcutaneous, every 24 h for 5 days) in sheep on biochemical parameters (n = 6, mean ± SD)

Parameters	0 h	48 h	120 h
ALB (g/dL)	2.97 ± 0.18	2.98 ± 0.29	2.98 ± 0.18
ALP (U/L)	58.83 ± 14.50	65.17 ± 21.14	68.00 ± 23.26
ALT (U/L)	26.00 ± 7.72	26.67 ± 7.28	28.17 ± 9.17
AST (U/L)	94.17 ± 11.62	96.83 ± 14.27	95.83 ± 9.97
BUN (mg/dL)	22.97 ± 2.87	20.87 ± 4.43	20.30 ± 2.89
CHOL (mg/dL)	67.50 ± 9.57	66.67 ± 11.34	62.17 ± 10.48
CK (U/L)	205.83 ± 23.64	181.33 ± 28.16	190.33 ± 34.99
CREAT (mg/dL)	0.60 ± 0.03	0.57 ± 0.08	0.52 ± 0.06
GGT (U/L)	47.00 ± 13.87	46.67 ± 13.06	47.33 ± 13.74
TP (g/dL)	6.63 ± 0.44	6.66 ± 0.68	6.58 ± 0.24
TG (mg/dL)	15.50 ± 3.56	18.33 ± 3.39	17.83 ± 2.93

ALB; albumin, ALP; alkaline phosphatase, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BUN; blood urea nitrogen, CHOL; cholesterol, CK; creatine kinase, CREAT; creatinine, GGT; gamma-glutamyltransferase, TP; total protein, TG; triglyceride.

Discussion

Drugs may cause adverse side effects. The side effects can be classified as pharmacological, biochemical, pathological, genotoxic, and allergic reactions. Hematological and biochemical parameters are used to evaluate the effects of drugs on physiological and pathological conditions (Maden et al., 2001; Altan et al., 2019). Hematological parameters (WBC, RBC, hemogram, hematocrit, platelet) reflect bone-marrow functions and fluid-electrolyte balance situations. Biochemical parameters (albumin, ALP, ALT, AST, BUN, cholesterol, CK, creatinine, GGT, TP, and triglyceride) reflect liver, kidney, muscle, and lipid

metabolism function (Turgut, 2000; Kerr, 2002a; Kerr, 2002b). Cephalosporins have a high therapeutic index and a very low incidence of adverse drug reactions. The adverse effects of cephalosporins, except for hypersensitivity, depend on the dose and duration of administration. Depending on the dose and duration of administration, cephalosporins cause neutropenia, thrombocytopenia, agranulocytosis, glomerular and interstitial nephritis, tubular necrosis, hepatitis, and neurotoxicity (Caprile, 1988; Maden et al., 2001).

In this study, the repeated administration of cefquinome via the subcutaneous route in sheep did not cause any change in hematological values. It has been reported that the IM administration of cefquinome to sheep (2 mg/kg, every 24 h for 5 days, Rana et al., 2015) and dogs (1 mg/kg, every 24 h for 14 days, Maden et al., 2001) causes no significant changes in hematological parameters. While the repeated (intravenous, every 12 h for 7 days) administration of cefquinome to horses at a dose of 1-6 mg/kg did not cause any change in WBC and platelet, the changes in RBC, hemoglobin, and hematocrit values were reported within reference values (Altan et al., 2019). In addition, the repeated (IM, 2 mg/kg, every 24 h for 7 days) administration of cefquinome in buffalo calves changed the hemoglobin value (Mangal et al., 2015).

In this study, the repeated administration of cefquinome subcutaneously in sheep did not cause any change in biochemical parameters. It has been reported that the repeated administration of cefquinome did not cause any change; in the values of ALT, AST, ALP, TP, albumin, glucose, and total bilirubin in the dogs (Maden et al., 2001); in the values of albumin, ALP, ALT, AST, cholesterol, creatinine, GGT, lactate dehydrogenase, total bilirubin, and TP in the horse (Altan et al., 2019); in the values of AST, ALT, ALP, urea, creatinine, albumin, and TP in the camels (Kant et al., 2019). While the repeated (2 mg/kg, IM, every 24 h for 7 days) administration of cefquinome did not cause any change in ALT, ALP, AST, and GGT activities in buffalo calves, it changed BUN and creatinine values (Mangal et al., 2015).

Conclusion

This study showed that subcutaneous administration of cefquinome at a dose of 2.5 mg/kg every 24 hours for 5 days did not affect hematological and biochemical parameters in sheep. However, there is a need for molecular and histopathological investigation of the safety of cefquinome after repeated administration in sheep at different doses and administration routes.

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Ethical Statement

The experiment was approved (2015/43) by the Ethics Committee of the Faculty of Veterinary Medicine of Şelcuk University (Konya/Turkiye) and carried out in accordance with the European Directive (2010/63/EU).

Conflict of Interest

The authors declared that there is no conflict of interest.

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