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Biochemical Alterations Following Repeated Intramuscular Administration of Cefquinome in Cow Calves During its Safety Assessment

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Abstract

The present study was carried out to investigate biochemical alterations induced after repeated intramuscular administration of cefquinome at the dose rate of 2 $mg.kg^{-1}$ body weight in five healthy cow calves during its safety assessment study. Blood samples were collected before administration of the drug which served as control (day 0). After administration of drugs, blood samples were collected at day 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 5^{th} and 6^{th} from jugular vein into vacutainers without K_3EDTA for serum biochemical parameters (serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum lactate dehydrogenase (LDH), serum alkaline phosphatase (AKP), serum acid phosphatase (ACP) and serum bilirubin) analysis. The results of the study clearly demonstrated that repeated intramuscular administration of cefquinome in therapeutic dose produced non-significant ($p<0.05$) difference in values of serum biochemical parameters in cow calves when compared with control values (0 day). Lack of clinical signs of adverse reactions and absence of significant difference in serum biochemical parameters following intramuscular administration of cefquinome, may open a new avenue for insight into the strategy for clinical treatment of various bacterial diseases in cow calves.

Keywords: Cefquinome, Cow calves, Safety study, Cephalosporin, Antibiotic.

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Introduction

Cefquinome, an aminothiazolyl fourth generation cephalosporin, has been developed solely for veterinary use. The advantages of cefquinome over the earlier cephalosporins include extended spectrum β-lactam activity, penetration ability into the periplasmic space of Gram-negative bacteria, enhanced binding with penicillin-binding proteins [3] stability against β-lactamases [9]and enhanced bioavailability and potency. The *in vitro* and *in vivo* efficacy of this drug against a wide range of Gram-negative and Gram-positive bacteria has been demonstrated by [9]. In veterinary medicine, cefquinome is approved and used for several animal species in many countries worldwide [1]. It has been approved in Europe for the treatment of respiratory tract diseases, acute mastitis and foot rot in cattle, calf septicemia, respiratory diseases in pigs, metritis-mastitis-agalactia syndrome in sows, foal septicemia and respiratory tract diseases in horses. Cefquinome is relatively safer antibacterial having fewer adverse effects than other cephalosporins. Owing to its high efficacy, broad spectrum of activity, rapid tissue penetration, high safety and very low development of bacterial resistance, cefquinome is gaining popularity among the practitioners. It's spectrum of activity and pharmacokinetic properties favour its use in veterinary practice. However, the data on safety of multiple

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intramuscular administration of cefquinome in cow calves are scarce. Biochemical alterations as a part of safety profile induced by cefquinome needs to be assessed before it is recommended for clinical application in treatment of infections caused by sensitive organism in cow calves. So present study was planned to investigate the biochemical alterations induced after intramuscular administration of cefquinome in cow calves.

Material and Methods

The present study was carried out on five healthy male cow calves of Gir breed (6-12 months and weighing between 70 to 120 kilograms) at Instructional Dairy Farm, College of Veterinary Science and Animal Husbandry, Mhow, Nanaji Deshmukh Veterinary Science University, Jabalpur (M.P.). The calves were housed in experimental calf pen, two weeks prior experiment for acclimatization. The animals were fed concentrates, green fodder and roughage and had free access to water. All essential and standard managemental measures were adopted to keep the calves free from stress. The animals were observed for any clinical abnormalities during the period of experiment. The study was approved by the Institutional Animal Ethics Committee (IAEC), College of Veterinary Science and Animal Husbandry, Mhow.

Drugs and chemicals

Cefquinome was gifted by Wellcon Animal Health Pvt. Ltd., Agra, India. Standard assay kits for serum biochemical analysiswere purchased from ERBA diagnostics Mannheim GmbH manufactured by Transasia Bio-medicals Ltd. Malpur, Baddi, Distt. Solan (H.P.), India.

Experimental design

Five healthy male cow calves were employed to assess the safety of intramuscular administration of cefquinome (2 $mg.kg^{-1}$b.wt., repeated at 24 hours interval) for 5 days. Blood samples were collected before administration of the drug which served as control (day 0). After administration of drugs, blood samples were collected at day 1st (24 h), 2nd (48 h), 3rd (72 h), 4th (96 h), 5th (120 h) and 6th (144 h) from jugular vein into vacutainers without K_3EDTA for serum biochemical analysis. Blood samples collected in vacutainers without K_3EDTA were allowed to clot at room temperature. Serum was harvested by centrifugation at 4000 rpm for 10 minutes at 4°C (Eppendorf 5804 R, Germany) and stored at –35°C for biochemical analysis. Serum from blood samples collected at predetermined time intervals was used to determine the following biochemical parameters viz. serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum lactate dehydrogenase (LDH), serum alkaline phosphatase (AKP), serum acid phosphatase (ACP) and serum bilirubin. All these biochemical parameters were estimated using standard assay kits (ERBA diagnostics Mannheim GmbH manufactured by Transasia Bio-medicals Ltd. Malpur, Baddi, Distt. Solan (H.P.), India, with the help of Biochemical analyzer (ErbaMeinheim E.M. 200, Transasia Bio-medicals Ltd. Germany) [15].

Statistical analysis

The data generated from the safety profile study were compared by Least Square Difference test using SPSS software (version 12.0.1).

Results

Values of the biochemical parameters (serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum lactate dehydrogenase (LDH), serum alkaline phosphatase (AKP), serum acid phosphatase (ACP), serum bilirubin, serum creatinine, blood urea nitrogen (BUN), total protein, albumin and blood glucose) before and after intramuscular administration of cefquinome (2 $mg.kg^{-1}$ b.wt., repeated at 24 h interval) for 5 days in cow calves are presented in Tables 01.

No significant alterations ($p<0.05$) in serum biochemical parameters, have been observed in the present study when compared with control values (0 day) following intramuscular administration of cefquinome (2 $mg.kg^{-1}$ b.wt., repeated at 24 h interval) for 5 days in cow calves. All animals were not exhibited any local or systemic adverse reactions after daily intramuscular administration of cefquinome.

Table 1: Effect of intramuscular administration of cefquinome (2 mg.kg^{-1} body weight, repeated at 24 hours interval) for 5 days on serum biochemical parameters in healthy male cow calves.

Serum Biochemical Parameters	Mean ± S.E.						
	0th Day	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day
AST (IU.L^{-1})	75.96 ± 2.14	73.67 ± 1.86	75.92 ± 1.86	74.69 ± 1.09	76.61 ± 1.96	77.08 ± 2.18	76.97 ± 2.14
ALT (IU.L^{-1})	31.05 ± 1.02	33.22 ± 1.24	32.08 ± 1.25	33.04 ± 1.28	34.01 ± 1.01	33.01 ± 0.85	32.01 ± 0.90
LDH (IU/L)	555.70 ± 5.56	557.31 ± 5.38	559.09 ± 6.16	555.38 ± 5.44	562.01 ± 6.29	557.05 ± 5.38	556.05 ± 5.34
AKP (IU.L^{-1})	116.63 ± 4.93	119.38 ± 4.60	116.90 ± 4.54	115.12 ± 3.64	118.23 ± 4.24	115.66 ± 3.97	116.22 ± 4.45
ACP (IU.L^{-1})	2.30 ± 0.12	2.44 ± 0.14	2.32 ± 0.06	2.36 ± 0.09	2.40 ± 0.12	2.32 ± 0.11	2.30 ± 0.10
Serum Bilirubin (mg.dl^{-1})	0.30 ± 0.01	0.28 ± 0.01	0.29 ± 0.02	0.32 ± 0.02	0.31 ± 0.01	0.30 ± 0.01	0.30 ± 0.02
Serum Creatinine (mg.dl^{-1})	1.25 ± 0.02	1.24 ± 0.02	1.24 ± 0.02	1.25 ± 0.01	1.24 ± 0.01	1.25 ± 0.02	1.24 ± 0.02
BUN(mg.dl^{-1})	15.44 ± 0.21	15.51 ± 0.31	15.60 ± 0.41	15.55 ± 0.25	16.21 ± 0.13	16.11 ± 0.22	15.94 ± 0.21
Total Protein (gm. dl^{-1})	6.67 ± 0.09	6.71 ± 0.10	6.69 ± 0.12	6.74 ± 0.13	6.72 ± 0.11	6.72 ± 0.12	6.68 ± 0.08
Albumin (gm.dl^{-1})	3.00 ± 0.06	2.98 ± 0.10	2.95 ± 0.10	3.05 ± 0.02	3.03 ± 0.06	3.05 ± 0.04	3.03 ± 0.07
Blood Glucose (gm.dl^{-1})	46.52 ± 1.31	45.81 ± 1.33	46.64 ± 0.93	44.78 ± 1.37	46.67 ± 1.09	47.27 ± 0.85	46.45 ± 0.98

All values in treatment groups are not significantly different ($p<0.05$) when compared to control (0 h).

Discussion

Antimicrobial therapy is usually employed to cure bacterial infection or to prevent the secondary bacterial infection. Prolonged therapy or high dosage regimen implemented during the treatment may exhibit the toxic effect, if any. Considering this fact, safety study of a drug is indeed necessary to notify any alteration in the physiological or biochemical parameters of the body fluid and tissue along with therapeutic effects. If alterations are very minor, the drug is relatively safe and if severe, then adverse effects of such drug will be observed. The effects of long term cefepime therapy on body systems were extensively evaluated in rats and dogs [5, 6]. In the present study safety of multiple intramuscular doses of cefquinome (2 mg.kg^{-1} body weight) repeated at 24 hours interval for 5 days in healthy cow calves was monitored by studying various biochemical parameters.

The Serum biochemical analysis included determination of various serum enzymes like serum asparate aminotransferase (AST), serum alanine aminotransferase (ALT), serum lactate dehydrogenase (LDH), serum alkaline phosphatase (AKP), serum acid phosphatase, serum bilirubin (total), total protein, albumin and blood glucose, during the course of treatments to evaluate patency of liver functions following multiple-dose intramuscular administration of cefquinome in cow calves. Similarly, serum creatinine and blood urea nitrogen levels were determined to monitor the patency of renal functions. In the present study, no significant alterations (p 0.05) in all serum biochemical parameters have been observed following daily intramuscular administration of cefquinome (2 mg.kg^{-1}b.wt. repeated at 24 h interval) for 5 days in healthy cow calves. It indicates that repeated long term administration of cefquinome was well tolerated in cow calves.

In agreement to the present findings, no significant alterations in all serum biochemical parameters following single intramuscular administration of cefquinome (2 mg.kg^{-1} b.wt., repeated at 24 h interval) along with intramuscular administration of tolfenamic acid (2 mg.kg^{-1} body weight) has been reported in sheep [13]. Similarly, it has been reported that multiple intramuscular doses of cefquinome (20 mg.kg^{-1} b.wt. repeated at 12 h) along with meloxicam (0.2 mg.kg^{-1} b.wt. repeated at 24 h) for 7 days in goats did not alter the serum biochemical parameters [16]. There was no significant changes in haematological and biochemical parameters following intramuscular

administration of cefpirome in combination with intramuscular administration of ketoprofen in goats [2]. There was no significant alterations in blood biochemical parameters following daily intramuscular administration of cefepime in combination with ketoprofen repeated at 12 hr interval for 5 days in goat [11]. It has been reported that at the dose of 1 $mg.kg^{-1}$, cefquinome did not affect haematological and biochemical values in dogs [10]. No significant alteration in all blood biochemical parameters except ALT and AST values measured at 108 and 120 h following repeated intravenous cefepime administration (20 $mg.kg^{-1}$)has been in sheep [12]. High dose cefoperazone administration has demonstrated hepatic and renal toxicity in laboratory animals. In contrast to present findings, the average organ weight including the liver, brain, lungs were decreased following cefepime therapy at the rate of 1500 $mg.kg^{-1}$ for 28 days in rats [5]. Reversible hepatomegaly [4] and hepatic damage with elevated ALT and AST have been noted during the cephalosporin therapy at higher dose rate [8]. Higher dose of cephalothin (>12 $g.day^{-1}$, total dose) was found to cause nephrotoxicity in rabbits [14]. Increase in kidney weights in F1 generation with no alteration in creatinine level in rats treated with cefepime at dose rate of 1000 mg kg^{-1} daily for 63 days has been noticed [7].

On the basis of observation of various serum biochemical parameters it is concluded that multiple intramuscular administration of cefquinome did not affect hepatic as well as renal functioning. This suggests that long term intramuscular administration of cefquinome is safe in cow calves. Thus it is advisable to use cefquinome at recommended dosage for treatment of infections not responding to conventional antibacterial drugs.

Conflict of Interest

None Declared

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