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Effects of multiple intramuscular administrations of cefpirome and flunixin meglumine on hemato-biochemical parameters in sheep

Vaidehi N Sarvaiya, Kamlesh A Sadariya, Shailesh K Bhavsar, Aswin M Thaker and Mohsin M Pathan

Abstract
Cefpirome, the fourth generation cephalosporin class of drug has excellent antibacterial activity against Gram-positive and Gram-negative organisms. Cefpirome is rapidly and widely distributed in body fluids and achieves excellent tissue concentrations which exceed the minimum inhibitory concentrations for most pathogens and recommended as the first line drug for febrile neutropenia. Flunixin meglumine, a non-steroidal anti-inflammatory drug used as adjunctive therapy in the treatment of sepsis in large and small ruminants. Treatment of infective condition with an antibacterial agent alone does not alleviate the inflammation, pain, swelling, fever and other complications that accompany an infective condition. Therefore the present study was undertaken to evaluate alteration in haematological and serum biochemical parameters following multiple intramuscular administration of cefpirome (10 mg/kg of body weight repeated at 12 hours interval) with flunixin meglumine (1.1 mg/kg of body weight repeated at 24 hours interval) in sheep for 5 consecutive days. The results indicated that there was no significant alterations in any of the haematological parameters evaluated, while significant ($p < 0.05$) alterations were observed in the mean values of serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) on 3rd, 4th and 5th day of drug administration; serum alkaline phosphatase (ALP) on 4th and 5th day of drug administration and total protein on day 4 of drug administration as compared to control (day 0). All the significant alterations were within their normal range. On the basis of observation of present study on various hematological and blood biochemical parameters, multiple intramuscular administrations of cefpirome along with intramuscular administration of flunixin meglumine did not affect normal body functioning and the combination is safe in sheep.

Keywords: Cefpirome, flunixin meglumine, hemato-biochemical, sheep

1. Introduction

The fourth generation cephalosporins such as cefepime, cefpirome and cefquinome have the widest spectrum of activity amongst the five groups. Due to zwitterions character of cefpirome, it has better penetration through the pore (porin protein) or channels of Gram-negative bacteria and rapidly binds to penicillin binding protein. Cefpirome also demonstrates excellent activity *in vitro* against pneumococci, including penicillin-resistant strains and as active as or more active than ceftazidime and cefotaxime against Enterobacteriaceae, *Haemophilus influenzae* and *Neisseria* spp. Cefpirome is rapidly and widely distributed in body fluids and achieves excellent tissue concentrations which exceed the minimum inhibitory concentrations for most pathogens. Cefpirome is recommended as the first line highly effective drug for febrile neutropenia. Cefpirome features a high level of safety and an extremely low risk of nephrotoxicity [1]. Basically, flunixin meglumine is utilized to control inflammation, pain and fever associated with various ailments. Flunixin meglumine used as adjunctive therapy in the treatment of sepsis in cattle, sheep, goat, dogs and horses [2].

Treatment of bacterial infections with an antibacterial agent alone does not alleviate the inflammation, pain, swelling, fever and other complications that frequently accompany an infective condition. Therefore, use of anti-inflammatory drugs with an antibacterial drug for prevention and treatment of a variety of disease is a common practice. Few non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, aspirin, celecoxib, carprofen, bromfenac and vedaprofen have been also shown to exhibit *in vitro* antibacterial activity against *E.coli* [3]. Synergistic interaction between NSAIDs and antibiotics presents a potential therapeutic option to treat infections with inflammatory conditions [4]. By taking all these facts in consideration, the present study was undertaken with the objective to evaluate alterations in haematological

ansd serum biochemical parameters following multiple intramuscular administration of cefpirome (10 mg/kg of body weight repeated at 12 hours interval for 5 days) in combination with flunixin meglumine (1.1 mg/kg of body weight repeated at 24 hours interval for 5 days) in sheep.

2. Materials and Methods

2.1 Experimental Animals

The animal experimentation in sheep (No. 306/VPT/2019) was approved by Institutional Animal Ethics Committee (IAEC) of Veterinary College, Anand, Gujarat, India. The study was conducted in six female Patanwadi sheep of 2-3 years of age weighing between 30 and 35 kilograms. The animals were maintained at the Livestock Farm Complex, Veterinary College, Anand. They were kept under constant observation for ten days prior to commencement of the experiment. During this period they were subjected to clinical examination in order to exclude the possibility of any disease. The animals were then housed in separate pens and were provided standard ration and *ad libitum* water.

2.2 Drugs, Chemicals and Reagents

For dosing purpose, Cefpirome sulfate (Bacirom® 1000 mg injection) was obtained from Aristo Pharmaceuticals Pvt. Ltd., Ahmedabad, Gujarat and flunixin meglumine (Megludyne® Injection, Virbac Animal Health Pvt. Ltd., Mumbai, India) was procured from local market.

2.3 Administration of Drugs and Blood Samples Collection

Six sheep were given cefpirome (10 mg/kg of body weight, IM, repeated at 12 hour intervals) with simultaneous administration of flunixin meglumine (1.1 mg/kg of body weight, IM, repeated at 24 hour intervals) for 5 consecutive days. Blood samples were collected before administration of the drug/s which served as control (day 0). After administration of drug/s, blood samples were collected at day 1, 2, 3, 4 and 5 from jugular vein (before administration of drugs) into sterile tubes for hematological and serum biochemical analysis. Blood samples (2 mL) collected in test tubes with K_3EDTA were utilized for hematological evaluation, whereas blood samples (3 mL) collected in centrifuge tubes without K_3EDTA were allowed to clot at room temperature. Serum was harvested by centrifugation at 2655 g for 10 minutes at 10ºC (Eppendorf 5804 R, Germany). Serum samples were stored at - 40ºC for biochemical analysis and analyzed within 12 hours.

2.4 Hematological Parameters

Blood samples collected in K_3EDTA vials at predetermined time intervals during course of experiment were used to evaluate parameters like total erythrocytes count (TEC), hemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), total leukocytes count (TLC), differential leukocytes count (DLC) (lymphocyte, monocyte, eosinophil, basophil and neutrophil) and platelets. These parameters were estimated using automated haematology analyzer (Exigo Veterinary Hematology Analyzer, Sweden).

2.5 Blood Biochemical Parameters

Harvested serum samples were utilized to determine various biochemical parameters like serum alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT), serum aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT), serum alkaline phosphatase (ALP), serum acid phosphatase (ACP), serum lactate dehydrogenase (LDH), serum total bilirubin (TB), serum total protein (TP), serum blood urea nitrogen (BUN), serum creatinine and serum glucose. All the biochemical parameters were estimated using standard assay kits (Coral Clinical Systems, A Division of Tulip Diagnostics (P) Limited, Goa) with the help of Clinical Biochemistry Analyzer (BS-120 Chemistry Analyzer, Shenzhen Mindray Bio-Medical Electronics Co. Limited, Shenzhen, China) as per manufacturer's protocol/method described in assay kit of respective biochemical parameters.

2.6 Statistical Analysis

All the data have been presented as Mean±SE. The data generated from safety study were analyzed by One-way analysis of variance (ANOVA) using software IBM SPSS (Version 20), where $p < 0.05$ was considered as statistically "significant".

3. Results and Discussion

3.1 Hematological Parameters

Values of various hematological parameters following intramuscular administration of cefpirome (10 mg/kg) in combination with intramuscular administration of flunixin meglumine (1.1 mg/kg) for 5 days in healthy sheep are presented in Table 1. The results of present study suggest that no significant difference was observed in any of the hematological parameters following multiple intramuscular administration of cefpirome (10 mg/kg) repeated at 12 hours interval in combination with intramuscular administration of flunixin meglumine (1.1 mg/kg) repeated at 24 hours interval for 5 days in healthy sheep. All the parameters were within their normal range. Similar to our study, non-significant alterations in hematological parameters have been reported in albino mice [5] and human [6]. While other authors have reported significant decrease in the mean hemoglobin level in rats [7] and human [8]. Decrease in red blood cell count has also been reported in toxicity study conducted for three months using cefpirome in rats [9].

3.2 Blood Biochemical Parameters

The mean values of various serum biochemical parameters following daily intramuscular administration of cefpirome (10 mg/kg) in combination with intramuscular administration of flunixin meglumine (1.1 mg/kg) for 5 days in healthy sheep are presented in Table 2. Various blood biochemical parameters like serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and bilirubin (total) were analysed to evaluate functional capacity of liver, while serum creatinine and blood urea nitrogen levels were determined to monitor the renal function. Additionally, levels of serum acid phosphatase (ACP), total protein (TP) and glucose were also measured to monitor metabolic status. Based on findings of present study, there was significant ($p < 0.05$) increase in the mean values of ALT and AST on 3rd, 4th and 5th day of administration of cefpirome and flunixin meglumine as compared to control (day 0), similar to that there was significant ($p < 0.05$) increase in the mean values of ALP on 4th and 5th day of drug administration as compared to control (day 0). There was significant ($p < 0.05$) decrease in the mean value of total protein on day 4 of drug

administration as compared to control (day 0). But these significant alterations were within their normal range. No significant alterations in other blood biochemical parameters were observed following intramuscular administration of cefpirome in combination with flunixin meglumine for 5 days in healthy sheep.

Similar to findings of present study, marginal increase in the mean values of ALT and AST while decrease in the mean value of total protein have been reported when cefpirome was orally administered (20 mg/kg, BID) for 7 days in male rats [7]. When repeated dose subacute toxicity study was conducted in rats at three different dose level (30, 60 and 120 mg/kg), non-significant alterations were observed in serum biochemical parameters at all three administered dose level [5]. Similarly, non-significant alterations have been observed in the level of serum creatinine, when 2 g cefpirome was administered at every 12 hours of interval for 7 days [10]; 2 g of cefpirome administered by intravenous route at every 12 hours of interval for 5 days [6] and 1 g of cefpirome was administered at every 12 hours of interval for 5 consecutive days [11] in human. While increase in the level of blood urea nitrogen, creatinine and uric acid after single intravenous administration of cefpirome at dose level of ≥ 500 mg/kg and in 14 and 21 days multiple intravenous administration of cefpirome at the dose level of ≥ 200 mg/kg, in Japanese white male rabbits have been reported [12]. Increase in the uric acid level when cefpirome was given at the dose rate of 0.8 g/kg body weight for three months in rats has been reported [9].

Table 1: Effect of intramuscular administration of cefpirome (10 mg/kg) repeated at 12 h and flunixin meglumine (1.1 mg/kg) repeated at 24 h interval for 5 days on haematological parameters in sheep (Mean±SE, n=6)

Time of treatment (Day)	TEC ($x10^6$/µL)	Hb (g/dL)	PCV (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	TLC ($x10^3$/ µL)	L (%)	M (%)	E (%)	B (%)	N (%)	Platelets ($x10^5$/ µL)
0	10.50±0.49	11.52±0.37	31.47±0.42	29.00±0.61	10.52±0.24	32.87±0.85	6.32±0.55	53.00±0.57	3.33±0.49	6.16±0.40	0.83±0.30	41.16±0.47	8.80±0.28
1st	11.01±0.78	11.30±0.30	31.54±0.35	29.80±0.52	10.42±0.33	33.93±0.64	6.51±0.35	53.83±0.47	3.50±0.42	6.33±0.49	0.66±0.33	40.66±0.49	8.89±0.59
2nd	10.75±0.46	10.46±0.42	32.05±0.59	30.20±0.66	10.62±0.38	32.95±0.66	6.40±0.41	52.66±0.33	3.66±0.49	7.33±0.33	0.83±0.40	41.83±0.60	9.05±0.72
3rd	10.30±0.29	10.60±0.27	32.53±0.42	30.40±0.48	10.70±0.21	33.45±0.37	6.47±0.42	53.16±0.40	4.00±0.36	6.00±0.36	0.50±0.22	41.33±0.42	9.13±0.37
4th	11.50±0.41	10.55±0.42	31.75±0.45	30.58±0.31	10.31±0.59	33.81±0.66	6.55±0.40	54.00±0.51	3.33±0.49	6.33±0.55	0.66±0.42	40.16±0.47	8.75±0.69
5th	11.32±0.37	11.21±0.54	32.38±0.30	29.12±1.01	11.02±0.68	33.05±0.39	6.38±0.49	53.00±0.36	4.16±0.40	7.00±0.36	0.33±0.21	41.00±0.77	9.25±0.50

TEC- total erythrocytes count, Hb- hemoglobin, PCV- packed cell volume, MCV- mean corpuscular volume, MCH- mean corpuscular hemoglobin, MCHC- mean corpuscular hemoglobin concentration, TLC- total leukocytes count, L- Lymphocyte, M- Monocyte, E- Eosinophil, B- Basophil and N- Neutrophil.

Table 2: Effect of intramuscular administration of cefpirome (10 mg/kg) repeated at 12 h and flunixin meglumine (1.1 mg/kg) repeated at 24 h interval for 5 days on serum biochemical parameters in sheep (Mean±SE, n=6)

Time of treatment (Day)	ALT (U/L)	AST (U/L)	ALP (U/L)	ACP (U/L)	LDH (U/L)	Bilirubin (mg/dL)	TP (g/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Glucose (mg/dL)
0	27.35±0.41^{a}	90.20±0.71^{ab}	130.80±0.52^{ab}	2.05±0.39	347.02±0.99	0.29±0.11	7.40±0.41^{b}	14.89±0.51	1.85±0.73	70.89±0.90
1st	27.05±0.63^{a}	91.50±0.41^{bc}	129.92±0.54^{a}	3.10±0.50	346.11±0.42	0.37±0.14	6.24±0.35^{ab}	15.77±0.59	1.66±0.54	69.33±0.44
2nd	26.39±0.50^{a}	89.71±0.47^{a}	131.55±0.67^{b}	2.70±0.53	348.23±0.48	0.28±0.08	7.52±0.89^{b}	15.22±0.99	2.01±0.33	71.24±0.49
3rd	30.04±0.73^{b}	92.03±0.60^{c}	130.67±0.43^{ab}	2.22±0.45	346.35±0.43	0.30±0.06	7.31±0.32^{b}	14.05±0.43	1.72±0.35	70.08±0.46
4th	31.17±0.38^{b}	95.15±0.39^{d}	134.70±0.42^{c}	3.01±0.47	347.27±0.51	0.33±0.09	5.20±0.72^{a}	14.21±0.39	2.60±0.86	71.10±0.64
5th	30.05±0.46^{b}	94.42±0.23^{d}	135.01±0.41^{c}	2.83±0.46	346.12±0.74	0.25±0.10	6.32±0.33^{ab}	15.32±0.50	1.01±0.18	69.35±0.33

[Mean values with dissimilar superscript (a, b, c) in a column vary significantly at $p < 0.05$] ALT- alanine aminotransferase, AST- aspartate aminotransferase, ALP- alkaline phosphatase, ACP- acid phosphatase, LDH- lactate dehydrogenase, TB- total bilirubin, TP- total protein, BUN- blood urea nitrogen.

4. Conclusions

On the basis of observation of present study on various hematological and blood biochemical parameters, multiple intramuscular administrations of cefpirome along with intramuscular administration of flunixin meglumine did not affect normal body functioning. This suggests that intramuscular administration of cefpirome along with flunixin meglumine for 5 consecutive days is safe in sheep. It is advisable to use combination therapy of cefpirome and flunixin meglumine at recommended dosage for treatment of infections not responding to other antibacterial drugs.

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