INFLUENCE OF PARACETAMOL ON THE PHARMACOKINETICS AND DOSAGE REGIMEN OF CEFTIZOXIME IN CROSS BRED CALVES

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ABSTRACT

Pharmacokinetics of ceftizoxime was investigated in cross-bred calves after a single intramuscular administration (10 $mg.kg^{-1}$) alone or co-administration with paracetamol. Concentration of ceftizoxime in plasma was estimated by microbiological assay technique using *E. coli* as the test organism. Following administration of ceftizoxime alone, the peak plasma level (C_{max} = 24.9 ± 1.11 $\mu g.ml^{-1}$) was attained at t_{max} of 45 min and the drug was detected in plasma above the minimum therapeutic concentration for up to 6 h post- administration. The disposition pattern of ceftizoxime followed the one-compartment open model. The values of absorption half-life, elimination half-life and AUC were 0.23 ± 0.03 h, 1.44 ± 0.12 h and 39.2 ± 2.09 $\mu g./ml^{-1}/h$. When co-administered with paracetamol, ceftizoxime attained a higher peak plasma level of 33.3 ± 1.78 $\mu g.ml^{-1}$, the drug was detected in plasma above the minimum therapeutic concentration up to 8 h post-administration, the disposition pattern followed the two-compartment open model and a significant increase was observed in the values of AUC (74.1 ± 2.01 $\mu g.ml^{-1}/h$) and $t_{1/2\beta}$ (4.08 ± 0.54 h). The study revealed that pharmacokinetics of ceftizoxime was altered by concomitant administration of paracetamol in cross-bred calves.

INTRODUCTION

Cephalosporins are among the most widely used group of antibacterials in veterinary and medical practice. Most third generation cephalosporins possess extended activity against pseudomonas spp. (1). Ceftizoxime is a third generation cephalosporin having high bactericidal activity against a wide range of gram-positive and gram-negative microorganisms including streptococci, staphylococci, proteus, bacillus, klebsiella, clostridium, salmonella and shigella (2). It is commonly used for the treatment of the infections of respiratory tract, urogenital tract, skin, soft tissues, bones and joints. Ceftizoxime has certain pharmacological and clinical advantages over other cephalosporins. It has better activity against anaerobes, broader spectrum of activity against gram negative bacteria (3) penetrates the cerebrospinal fluid in sufficient concentration due to greater lipid solubility (4) and is resistant to hydrolysis by β-lactamase (5) ceftizoxime is not metabolized in the body, and is excreted predominantly by glomerular filtration (6). In veterinary practice, the trend of multiple drug therapy has increased many fold due to several practical complexities in the diagnosis of diseases. Antibacterials and analgesic drugs are used most frequently in multiple prescriptions. It is well documented that concurrently administered drugs may affect the absorption, distribution, biotransformation and excretion of one or both (7). The co-administration of NSAIDs with cephalosporins has been associated with pharmacokinetic interactions (8). Paracetamol a non-narcotic analgesic, antipyretic agent is routinely used in veterinary practice (9) and has been reported to alter the disposition of cephalosporins (10). The pharmacokinetic profile of ceftizoxime following intravenous (iv) administration has been investigated in healthy and febrile calves (11, 12), healthy and nephropathic goats (13) mice, rats, dogs, and monkeys (14). However, there is no information available on the influence of simultaneously administered paracetamol on the pharmacokinetic behavior of ceftizoxime in animals. In view of the paucity of pharmacokinetic data on interaction of paracetamol with antibacterials in bovines, this study was undertaken to determine the pharmacokinetics and an appropriate dosage regimen of ceftizoxime in cross-bred calves after a single intramuscular (im) administration alone and following co-administration with paracetamol.

MATERIALS AND METHODS

Experimental animals and drug administration

The study was conducted on eight male cross-bred calves of about one year old and weighing 74-108 kg. The animals were acclimatized to the experimental conditions for 2 weeks prior to the commencement of the experiment. During the experimental period, the animals were maintained on green fodder and wheat straw and water was provided *ad libitum*. The average day temperature in the shed was about 25°C during the experiment. The experimental protocol followed the ethical guidelines on the proper care and use of animals. The animals were divided into two groups of four animals each. Ceftizoxime (Ceftizox, Burroughs Wellcome, India) was administered by im injection into the lateral neck region of both groups of calves at the dose rate of 10 $mg.kg^{-1}$ as freshly prepared 10 % solution. In animals of group 2, paracetamol (Paracetol-Vet, Cadila Health Care, India) was administered at a dose rate of 50 $mg.kg^{-1}$ by single i/m injection at a separate site immediately prior to administration of ceftizoxime.

Collection of samples

Blood samples (6 ml) were collected into heparinized glass centrifuge tubes by jugular venipuncture at different time intervals viz. 1, 2.5, 5, 7.5, 10, 15, 30 and 45 min/ and at 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9 and 10 h of administration of ceftizoxime. Plasma was separated by centrifugation at 1300 g and stored at –20 °C until analyzed for ceftizoxime, which was usually done on the day following collection.

Analytical method

Concentration of ceftizoxime in plasma was estimated by microbiological assay (15) using *Escherichia coli* (ATCC 25922) as the test organism. The assay could detect a minimum of 0.05 $\mu g.ml^{-1}$ of ceftizoxime. The concentration of paracetamol in plasma was determined by a spectrophotometric method based on the absorbance of nitrated paracetamol (4'-hydroxy-2'-nitroacetanilamide) in alkaline medium at 430 nm (16).

Pharmacokinetic analysis

The concentrations of ceftizoxime in plasma were plotted on a semi-logarithmic scale as a function of time and the pharmacokinetic parameters were calculated manually for each animal by least square regression (17). The differences between two means based on individual observations were determined by student's t-test. The significance was assessed at 1 and 5 % levels (18).

RESULTS

The plasma levels of ceftizoxime at different time intervals following a single intramuscular injection given alone or after intramuscular administration of paracetamol are presented on semilogarithmic scale in Figure 1. The plasma concentration of ceftizoxime at 1 min after the single intramuscular injection was 1.04 ± 0.15 $\mu g.ml^{-1}$, which gradually increased and the peak plasma concentration (24.9 ± 1.11 $\mu g.ml^{-1}$) was observed at 45 min. The drug levels above the minimum inhibitory concentration (MIC) were detected in plasma up to 6 h. A concentration of 0.004-1.0 $\mu g.ml^{-1}$ of plasma has been reported as the MIC for cephalosporins with various pathogens (19). However, in the present discussion, the higher concentration of 1.0 $\mu g.ml^{-1}$ was considered as the ceftizoxime MIC. On concurrent administration of paracetamol and ceftizoxime, the plasma levels of paracetamol (> 10.0 $\mu g.ml^{-1}$) were achieved within 1 min and persisted up to 4 h post-injection. When administered concurrently with paracetamol, the initial plasma concentration of ceftizoxime at 1 min was 1.36 ± 0.16 $\mu g.ml^{-1}$, which increased to attain the peak plasma concentration (33.3 ± 1.78 $\mu g.ml^{-1}$) at 45 min. Drug levels above the MIC were detected in plasma up to 8 h. Various kinetic determinants that describe the absorption and elimination pattern of ceftizoxime after intramuscular injection either used alone or in combination with paracetamol were calculated and are presented in Table 1.

DISCUSSION

The evaluation of the results on observed plasma levels of ceftizoxime administered alone indicated that the data can be best fitted to one-compartment open model and the pharmacokinetics was described by the equation: $C_P = Be^{-\beta t} - Ae^{-kat}$. Mono-compartment model has also been used to describe the disposition pattern of ceftizoxime after i/m administration in goats (13). The rapid appearance of ceftizoxime in plasma suggested that this drug rapidly entered the systemic circulation following im administration. Perusal of kinetic determinants of ceftizoxime following im administration alone revealed a high value of absorption rate constant, Ka (3.20 ± 0.37 h^{-1}) further confirming that after im administration, its absorption is very quick. Rapid absorption after im injection has also been reported for another third generation cephalosporin, cefotaxime in crossbred calves (20). The high value of AUC (39.2 ± 2.09 $\mu g.ml^{-1}/h$) after im administration in the present study reflected a vast area covered under drug concentration. High AUC value was also shown for ceftizoxime in calves (42.7 $\mu g.ml^{-1}/h$), goats (26.7 $\mu g.ml^{-1}/h$), dogs (100 $\mu g.ml^{-1}/h$) and monkeys (56.2 $\mu g.ml^{-1}/h$) after i/v injection (12, 13, 14). The elimination of ceftizoxime was rapid with a $t_{½}$ of 1.44 ± 0.12 h following its im administration alone in crossbred calves. Short elimination half-life of ceftizoxime has also been reported as 1.64 h in goats after im administration (13) and 1.73 h in calves, 0.27 h in mice, 0.3 h in rat, 1.06 h in dog and 0.84 h in monkeys following iv administration (12, 14).

When co-administered along with paracetamol, ceftizoxime attained a higher peak plasma level and the drug was detected in plasma above the minimum therapeutic concentration for a longer duration. The disposition pattern followed the two-compartment open model. A significant increase was observed in the value of AUC (74.1 ± 2.01 $\mu g.ml^{-1}.h$) indicating the greater area under drug concentration as compared to ceftizoxime when given alone. The present finding was in accordance to the observation in calves wherein paracetamol was found to increase the AUC of levofloxacin on concurrent administration

(21). The higher value of elimination half-life (4.08 ± 0.54 h) compared to the value of $t_{1/2\beta}$ obtained when giving ceftizoxime alone reflected its lower elimination than on co-administration with paracetamol in calves. Consistent to the present results, paracetamol has been shown to increase the elimination half-life of oxytetracycline in goats (22).

Speculation concerning the mechanism of interaction between NSAIDs and antibacterials has focused on drug absorption, distribution, metabolism and elimination. Several drugs are known to alter the hepatic metabolism of other drugs by enzyme induction or inhibition. Unlike most other cephalosporins, ceftizoxime is not metabolized in the body and is excreted unchanged in urine (23). However, slower elimination and clearance has been demonstrated for ceftizoxime during renal impairment (24). NSAIDs are known to precipitate renal failure in hepatic disease (25), and inhibit renal production of prostaglandins eventually leading to renal dysfunctions (26). Portal hypertension may lead to low peripheral resistance and hyperdynamic circulation due to increased production of vasodilating substances such as nitric oxide (27). The observed effect of paracetamol on the pharmacokinetics of ceftizoxime may be due to alteration in the rate of drug elimination from body. Further, paracetamol has been shown to induce the ATP-dependent drug transporter, MRP4 in mice (28). This multidrug resistance-associated protein 4 (MRP4) is involved in the tubular secretion of ceftizoxime and some other drugs in concert with basolateral uptake transporters (29). Such up regulation of MRP4 protein by paracetamol may be a possible mechanism for the alteration in the pharmacokinetics of ceftizoxime by paracetamol. In accordance to the present findings, significant effect of paracetamol has been reported on the pharmacokinetic parameters of cefotaxime (10) and levofloxacin (21) in calves and oxytetracycline in goats (22). Based on the results, it can be concluded that the pharmacokinetics of ceftizoxime was altered by concomitant administration of paracetamol in cross-bred calves.

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Table 1: Comparative pharmacokinetics of ceftizoxime (10 mg. kg^{-1}) after intramuscular injection alone and in combination with paracetamol (50 mg. kg^{-1}) in calves (n=4)

Parameter	Unit	Ceftizoxime	Ceftizoxime and Paracetamol
A'	$\mu g.\ ml^{-1}$	24.1 ± 4.63	54.8 ± 6.32*
Ka	h^{-1}	3.20 ± 0.37	3.31 ± 0.27
$t_{½Ka}$	h	0.23 ± 0.03	0.21 ± 0.02
B	$\mu g.\ ml^{-1}$	24.0 ± 4.47	5.19 ± 1.70*
β	h^{-1}	0.49 ± 0.05	0.18 ± 0.03*
$t_{1/2\beta}$	h	1.44 ± 0.12	4.08 ± 0.54*
AUC	$\mu g.\ ml^{-1}.h$	39.2 ± 2.09	74.1 ± 2.01**
C_{max}	$\mu g.\ ml^{-1}$	24.9 ± 1.11	33.3 ± 1.78**
t_{max}	h	45.0 ± 0.0	45.0 ± 0.0

Statistically significant * ($p<0.05$), ** ($p< 0.01$)

A and B = zero-time plasma drug concentration intercepts of the regression lines of absorption and elimination phases, respectively; Ka and β = absorption and elimination rate constants, respectively; $t_{½Ka}$ = absorption half-life; $t_{½\beta}$ = elimination half-life; AUC = area under the plasma concentration-time curve; C_{max} and t_{max} = peak plasma drug concentration and time required to attain the peak concentration, respectively.

LEGEND TO FIGURE

Fig.1 Semilogarithmic plot of plasma concentration-time profile of ceftizoxime following a single intramuscular injection of 10 mg.kg^{-1} body weight alone and in combination with paracetamol (50 mg. kg^{-1}) in calves. Values are presented as mean ± SE of 4 animals. The data was analysed according to one - compartment open model for ceftizoxime alone and two - compartment open model for ceftizoxime in combination with paracetamol.