

Meloxicam co-treatment alters pharmacokinetics of ceftizoxime in febrile sheep

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Received: 25 January 2010; Accepted: 12 November 2010

Key words: Ceftizoxime, Drug-interaction, Meloxicam, Pharmacokinetics

Meloxicam, an enolic acid class non-steroidal anti-inflammatory drug (NSAID), preferentially inhibits inducible cyclooxygenase-2 (COX-2) over COX-1 and have anti-inflammatory, analgesic and antipyretic activities (Euler-Ziegler and Velicitat 2001). Ceftizoxime (CZX) is a semi-synthetic, β -lactamase resistant, third generation cephalosporin with broad spectrum antibacterial activity (Richards and Heel 1985). Combined use of antibiotics and NSAID is very common in veterinary practice (Deleforge *et al.* 1994). Concurrent use of meloxicam alters the pharmacokinetics of certain drugs, like furosemide and levofloxacin (Muller *et al.* 1997, Dumka *et al.* 2008). Pharmacokinetics of ceftizoxime as well as meloxicam alone in sheep was investigated (Rule *et al.* 2000, Shukla *et al.* 2007). Certain NSAID like paracetamol was reported to alter the disposition of ceftizoxime in calves (Singh *et al.* 2008). However, the effect of meloxicam co-treatment on pharmacokinetics of ceftizoxime has not been investigated so far. Pyrexia, an important clinical sign, is observed in a variety of infectious diseases in sheep. Since combination therapy with meloxicam and ceftizoxime is warranted in febrile conditions, the present study aimed to study the effects of meloxicam co-treatment on ceftizoxime pharmacokinetics in febrile sheep.

Female sheep of Chhotanagpuri breed, 2 to 2.5 years old with 12 to 14 kg body weight, were dewormed and acclimatized for 30 days in experimental animal shed before starting the experiment. They were fed balanced ration and green fodder. The experiment was conducted as per the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals, Government of India. Animals (n=12) were randomly divided into 2 equal groups (groups 1 and 2). Fever was induced by intravenous administration of *E. coli* serotype 0126: B8 lipo-

polysaccharide (LPS). LPS was dissolved in pyrogen free sterile water to make a solution containing 1 μ g LPS/ mL and given intravenously @ 0.2 μ g/ kg body weight. After 5 h, half of the initial dose was repeated to maintain the fever. After 1h of LPS administration, group 1 animals received single intravenous injection of CZX @ 25 mg/kg body weight, while group 2 animals received single intravenous doses of CZX @ 25 mg/kg and meloxicam @ 0.5 mg/kg body weight. From each animal, about 2 ml of blood sample was collected in heparinized vial by jugular venipuncture at 0.04, 0.08, 0.16, 0.25, 0.33, 0.50, 0.75, 1, 2, 3, 4 and 6 h interval. Blood samples were brought to the laboratory, plasma was separated and stored at -20°C until drug analysis. Plasma CZX concentration was estimated by high performance liquid chromatography (Facca *et al.* 1998). The limit of quantization was 1.25 μ g/ml and mean ($\pm$ SE) absolute recovery of CZX was $83.83 \pm 1.15\%$. The intra-assay and inter-assay coefficients of variation were 7.67 and 9.0 respectively. The theoretical zero time plasma drug concentration, half life of distribution phase and half life of elimination phase were calculated using formulae suggested by Baggot (1977). The area under the plasma concentration curve and the mean residual time were calculated by the method of Raoff and Sams (1985). The volume of distribution in total area under curve, total body clearance, rate of diffusion from peripheral compartment to central compartment and rate of diffusion from the central to peripheral compartment were calculated as per Notari (1980). Different pharmacokinetic parameters were statistically analyzed using Student t-test (Snedecor and Cochran 1994).

In the present study, the plasma concentration-time profile of CZX evidenced biexponential disposition curve and hence best fitted to a 2 compartment open model (Fig. 1). Plasma CZX concentration in animals co-treated with meloxicam (group 2) remained higher than animals given CZX alone (group 1) throughout the observation period. Only one deviation from this trend was observed after 0.04 h of drug administration. In both groups, plasma drug concentrations reached below the detection level after 3 h of drug administration. There could be several possible reasons

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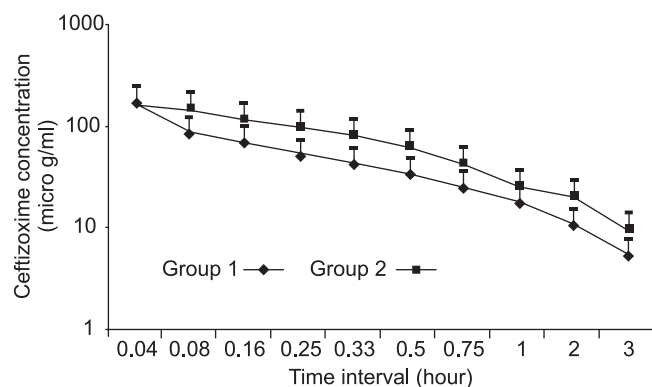


Fig 1. Semilogarithmic plot of plasma ceftizoxime (CZX) concentration versus time in febrile sheep given only CZX (group I) and CZX along with meloxicam (group 2)

behind higher plasma CZX concentration in group 2 animals. Plasma protein binding of CZX is only 52% (Shakthidevan *et al.* 2005) against 99% of meloxicam (Euller-Ziegler *et al.* 2001). Therefore, it may be possible that meloxicam replaced CZX from the plasma protein binding sites leading to increase in free CZX in plasma. However, role of some other factors, like differences in pKa value, pH of the medium and ionization extent can not be ruled out at this stage. Pharmacokinetic analysis revealed that only $t_{1/2\beta}$ did not differ significantly in between the 2 groups (Table 1). Thus it is obvious that meloxicam had no effect on half life of elimination phase. However, the overall elimination rate constant (β) was significantly ($P < 0.01$) lower (12.05%) in group 2. The metabolites of CZX may be one of the reasons for increase or decrease of plasma levels of CZX. But, in the present study, the role of CZX metabolites on plasma CZX concentration could not be pinpointed since their identification and measurement was not undertaken. Distribution of drug begins, as soon as it enters to blood circulation and is completed when the drug has reached all possible sites. Obviously, the volume of distribution in area under curve ($V_{d_{area}}$) depends on physiochemical properties of the drug. In the present study, $V_{d_{area}}$ in group 2 was 27.03% lower than group I. It may be possible that administration of meloxicam along with CZX affected the distribution of drug and most of the drug (CZX) remained in systemic circulation and were not transferred in other body fluids. Probencid co-treatment was reported to alter the pharmacokinetics of CZX (Le Bel *et al.* 1983). It increased the area under the serum concentration time curve by 49%. In the present study also, AUC of CZX was about 60.94% higher in animals co-treated with meloxicam in comparison to animals given CZX alone. Higher (60%) half-life of elimination phase in group 2 further substantiated this hypothesis. In the present study Cl_B was 34.88% lower in group 2 animals. Value of Cl_B depends on rate of blood flow and concentration of drug (Baggot 1977). Therefore, it may be possible that administration of meloxicam along with CZX might have decreased hepatic

Table 1. Effect of meloxicam co-treatment on pharmacokinetic parameters of ceftizoxime in febrile sheep

Parameter	Group I	Group 2
A ($\mu\text{g/ml}$)	359.29 $\pm$ 13.00	101.01 $\pm$ 2.31*
B ($\mu\text{g/ml}$)	57.08 $\pm$ 3.25	80.32 $\pm$ 3.33**
C ^o p ($\mu\text{g/ml}$)	416.36 $\pm$ 10.98	181.33 $\pm$ 2.92**
α (h^{-1})	29.36 $\pm$ 0.35	4.92 $\pm$ 0.21**
β (h^{-1})	0.83 $\pm$ 0.04	0.73 $\pm$ 0.03**
$t_{1/2\alpha}$ (h)	0.02 $\pm$ 0.00	0.14 $\pm$ 0.01**
$t_{1/2\beta}$ (h)	0.84 $\pm$ 0.04	0.95 $\pm$ 0.03
AUC(mg/L.h)	80.90 $\pm$ 2.38	130.20 $\pm$ 4.65**
MRT (h)	1.02 $\pm$ 0.04	1.21 $\pm$ 0.05**
Cl_B (ml/kg/min)	5.16 $\pm$ 0.15	3.36 $\pm$ 0.10**
$V_{d_{area}}$ (L/kg)	0.37 $\pm$ 0.02	0.27 $\pm$ 0.01**
K_{21} (h^{-1})	4.78 $\pm$ 0.37	2.58 $\pm$ 0.11**
K_{12} (h^{-1})	20.26 $\pm$ 0.26	1.68 $\pm$ 0.10**
K_{el} (h^{-1})	5.16 $\pm$ 0.15	1.39 $\pm$ 0.05**
P/C	5.29 $\pm$ 0.39	0.91 $\pm$ 0.05**

* $P < 0.05$; ** $P < 0.01$

Group I, ceftizoxime alone; group 2: ceftizoxime and meloxicam. Abbreviations: A, zero time drug concentration at distribution phase; B, zero time drug concentration at elimination phase; α , regression coefficient for distribution phase; β , regression coefficient for elimination phase; C^op, theoretical zero time plasma drug concentration; $t_{1/2\alpha}$, half life of distribution phase; $t_{1/2\beta}$, half life of elimination phase; AUC, area under the plasma concentration curve; MRT, mean residual time; Cl_B , total body clearance; $V_{d_{area}}$, volume of distribution in total area under curve; K_{21} , rate of drug diffusion from peripheral to central compartment; K_{12} , rate of drug diffusion from the central to peripheral compartment; K_{el} , elimination rate constant from central compartment; P/C ratio, peripheral/central compartment drug concentration ratio.

blood flow. However, in a study, Lode *et al.* (1983) observed much higher value of Cl_B (151.00 $\pm$ 33.00 ml/kg/min) for CZX. This may be due to multiple doses of CZX given in that experiment as well as species variation in drug metabolism. The P/C ratio observed in the study indicated that the distribution of the drug to various tissues in both groups were sufficient to combat the infection (Ahangar *et al.* 2000). Higher value of P/C ratio in group 1 suggested that higher CZX concentration was present in peripheral compartment of animals given CZX alone. This may be due to reduced tissue distribution of CZX in meloxicam co-treated animals. However, the mean values of P/C ratio observed in the present investigation were much lower than T/P ratio (10.24 $\pm$ 1.46) for ceftriaxone in febrile buffalo calves (Dardi *et al.* 2005).

From the present study, it can be concluded that meloxicam co-treatment enhances the plasma CZX concentration possibly by reducing its tissue distribution. Therefore, concurrent administration of meloxicam may help in rapid recovery from diseases where higher bacterial burden in blood is observed.

SUMMARY

Effect of meloxicam co-treatment on pharmacokinetic parameters of ceftizoxime (CZX) in *E coli* LPS induced febrile sheep (n=12) was studied. Group 1 (n=6) animals received single intravenous injection of CZX @ 25 mg/ kg body weight, while group 2 animals (n = 6) received CZX @ 25 mg/ kg body weight along with single intravenous dose of meloxicam @ 0.5 mg/ kg body weight. Plasma drug concentration-time profile in both groups evidenced a biexponential disposition curves and best fitted to two compartment open model. Plasma CZX concentrations in group 2 remained higher than group 1 throughout the observation period. In both groups, plasma CZX concentration reached below detection level after 3 h of drug administration. Half-life of elimination phase did not differ significantly in between the two groups. However, zero time drug concentration at distribution phase, theoretical zero time plasma drug concentration, half-life of distribution and elimination phases, total body clearance, rate constants of drug diffusion from peripheral to central and central to peripheral compartment, elimination rate constant from central compartment and peripheral/ central compartment drug concentration ratio were significantly lower in group 2. Other parameters, like zero time drug concentration at elimination phase, area under plasma concentration curve and mean residual time were significantly higher in group 2. Our results revealed that meloxicam co-treatment enhances the plasma CZX concentration possibly by reducing tissue distribution of the drug.

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