

Modification of pharmacokinetics of cefotaxime in uranyl nitrate-induced renal damage in black bengal goats

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Pharmacokinetics of cefotaxime (50 mg/kg, i.m.) were studied in both healthy and kidney damaged female black Bengal goats. Uranyl nitrate (0.75 mg/kg) was administered intravenously, once daily for five consecutive days to induce kidney damage. The pharmacokinetic variables were calculated in both cases. Kidney damage caused several changes in the determined variables. The C_{max} and C_{min} of cefotaxime observed at 0.50 and 5 h in normal goats were 24.91 ± 1.51 and 1.22 ± 0.07 $\mu\text{g/ml}$, respectively, while the same in kidney damaged goats at 1 and 72 h were 75.00 ± 0.45 and 3.10 ± 0.09 $\mu\text{g/ml}$, respectively. Renal damage condition significantly increased $t_{1/2,ka}$ (0.48 ± 0.01 h), $t_{1/2,ke}$ (20.03 ± 0.16 h), AUC (2440.10 ± 24.26 $\mu\text{g. h/ml}$) and significantly decreased $V_{d,area}$ (0.59 ± 0.007 L/kg), V_{ss} (0.58 ± 0.007 L/kg) and Cl_b (0.02 ± 0.008 L/kg/h) values of cefotaxime compared to normal goats.

Key words: pharmacokinetics, cefotaxime, kidney damage, goats

Introduction

Cefotaxime, a third generation cephalosporin derivative, possesses a wide range of anti-microbial activity against both gram positive and gram negative bacteria, and thereby claims superiority over many other antibiotics. It is extensively used in animals for treating systemic infection like pyelonephritis, embolic nephritis and nephrosis. Though the reports of cefotaxime kinetics in healthy animals are available [1] but the effects of cefotaxime on kinetics are scarcely available in kidney damaged goats. Therefore, the present study, investigates the alteration of disposition kinetics of cefotaxime in healthy and kidney damaged goats following single intramuscular administration.

Materials and Methods

Cefotaxime sodium was used as the test drug. All the chemicals used for the experiment were obtained from E. Merck (India), Loba Chemicals Ltd. (India) and Sigma Chemical Co. (USA)

Six clinically healthy adult black Bengal female goats weighing between 10-12 kg were utilized in this experiment. The animals were kept in individual custom made stainless steel cage (48" \times 48" \times 36") in a temperature ($22 \pm 2^\circ\text{C}$) controlled animal room having provision of artificial light. They were acclimatized with the laboratory condition for 7 days. They were fed with balanced feed and water was supplied *ad libitum*. The animals were dewormed with levamisole at 7.5 mg/kg 30 days prior to the onset of study. The lower part of the neck of each animal was shaved and the jugular vein was exposed. The animals were kept overnight fasting prior to the start of experiment. All procedure involved in the study were approved by the Animal Ethical Committee of West Bengal University of Animal and Fishery Sciences.

Cefotaxime sodium dissolved in 5 ml of pyrogen free distilled water was administered intramuscularly in the thigh region at 50 mg/kg. The blood samples (2 ml each) were collected from the left jugular vein separately in heparinized test tubes at 0, 0.08, 0.16, 0.33, 0.50, 0.66, 1, 2, 3, 4, 5, 6, 8, 10 and 12 h of post drug administration.

Plasma was separated by centrifugation at 3000 rpm for 20 min and stored at 4°C in refrigerator. One ml plasma was utilized for estimation of cefotaxime concentration.

After a period of rest for one month, uranyl nitrate crystals dissolving in distilled water was administered at 0.75 mg/kg once daily for five consecutive days by jugular veinipuncture to induce kidney damage [2]. Intensity of damage was ascertained by monitoring blood urea nitrogen and plasma creatinine levels every 24 h starting from 0 h to 144 h (6 days).

Cefotaxime at 50 mg/kg was administered by deep intramuscular route (thigh muscle) to each goat after 24 h of last dosing of uranyl nitrate administration (6th day) and

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blood samples (2 ml each) were collected from left jugular vein at 0, 0.08, 0.16, 0.33, 0.50, 0.66, 1, 4, 8, 12, 24, 36, 48, 60, 72, and 84 h for estimation of cefotaxime.

Cefotaxime was estimated by the modified method described by Jha *et al.* [3]. The final volume of each aliquot in test tube was 4 ml containing 1 ml plasma and 3 ml isopropyl alcohol in 0.05% of glacial acetic acid. Each test tube was shaken vigorously for 5 min, allowed to stand for 5 min and then centrifuged at 3000 rpm for 30 min. The supernatant was collected and analyzed in the UV-Vis spectrophotometer at 295 nm against blank prepared with plasma collected at 0 h. Concentration of cefotaxime present in each blood sample was then calculated from standard curve prepared earlier and expressed as mg/ml. The minimum sensitivity of this method was 1 mg/ml.

Blood urea nitrogen and plasma creatinine levels were estimated colorimetrically [4].

Students *t*-test was applied to test the level of significance in drug concentration and kinetic parameters in different groups of animals.

Results

Mean plasma concentration of cefotaxime at different time interval after single dose intramuscular administration at 50 mg/kg in healthy goats has been incorporated in Fig. 1. Cefotaxime could be detected in plasma of goats at 0.08 h ($19.17 \pm 1.07 \mu\text{g/ml}$) followed by increase in concentration and achieved a maximum concentration ($24.91 \pm 1.51 \mu\text{g/ml}$) at 0.50 h and thereafter the concentration of drug started to decline. The minimum concentration was recorded ($1.22 \pm 0.07 \mu\text{g/ml}$) at 5 h post dosing (pd). The plasma concentration of cefotaxime was below the detection level at 6 h pd.

The disposition kinetic parameters of cefotaxime in goats after i.m. administration have been presented in Table 1. Table 1 shows that the mean value of zero time plasma concentration (C_0) was found to be $56.13 \pm 3.60 \mu\text{g/ml}$. The k_a and k_e values were 4.51 ± 0.27 and $0.68 \pm 0.01 \text{ h}^{-1}$, on the other hand $t_{1/2k_a}$ and $t_{1/2k_e}$ values were 0.16 ± 0.01 and $1.03 \pm 0.02 \text{ h}$, respectively (Table 1). The $V_{d_{\text{area}}}$, V_{ss} and V_{d_c} values were 1.33 ± 0.09 , 1.23 ± 0.09 and $0.92 \pm 0.06 \text{ L/kg}$, respectively. The k_{21} and k_{e1} values were 1.13 ± 0.13 , 3.07 ± 0.13 and $0.99 \pm 0.02 \text{ h}^{-1}$, respectively. The f_c and T~P values were 0.69 ± 0.01 and 0.46 ± 0.02 .

Mean plasma concentration of cefotaxime at different time intervals after single dose i.m. administration at 50 mg/kg in kidney damaged goats were presented in Fig. 1. Cefotaxime could be detected in the plasma of goats at 0.08 h ($34.00 \pm 0.58 \mu\text{g/ml}$), which then gradually increased along with time, attained the peak level at 1 h; almost maintained a plateau till 24 h and then slowly declined till 72 h pd. The concentration of cefotaxime was minimum at 72 h ($3.10 \pm 0.09 \mu\text{g/ml}$) pd, and could not be detected

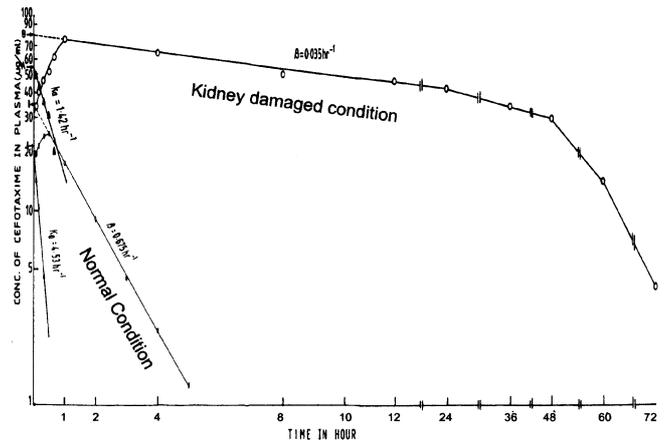


Fig. 1. Semilogarithmic plot of mean plasma concentration of cefotaxime against time following single dose, i.m., administration @ $50 \text{ mg kg}^{-1} \text{ b.w.}$ to normal and kidney damaged goats.

thereafter. Cefotaxime persisted in blood of kidney damaged goats for a longer period with higher concentration compared to normal goats.

The kinetic parameters of cefotaxime in kidney damaged goats after i.m. administration are shown in Table 1. Table 1 reveals that mean value of plasma concentration at zero time (C_0) was $139.77 \pm 1.60 \mu\text{g/ml}$. More than two and half-fold increase of plasma concentration at zero time was observed in kidney damaged goats compared to normal goats. The k_a and $t_{1/2k_a}$ values were $1.46 \pm 0.03 \text{ h}^{-1}$ and $0.48 \pm 0.01 \text{ h}$, respectively (Table 1). The lower k_a along with higher $t_{1/2k_a}$ values indicated slow rate of absorption of drug in kidney damaged goats compared to normal goats (k_a , $4.51 \pm 0.27 \text{ h}^{-1}$; $t_{1/2k_a}$, $0.16 \pm 0.008 \text{ h}$). The k_e and $t_{1/2k_e}$ values were $0.04 \pm 0.001 \text{ h}^{-1}$ and $20.03 \pm 0.16 \text{ h}$, respectively. The k_e values was very poor while $t_{1/2k_e}$ value was twenty times larger than that of normal goats. Likewise, Cl_B and k_{sl} values were $0.02 \pm 0.008 \text{ L/kg/h}$ and $0.06 \pm 0.001 \text{ h}^{-1}$ which were significantly lower than that of the values of normal goats.

Discussion

The maximum concentration of cefotaxime was recorded at 0.5 h following intramuscular administration to healthy goats. Atef *et al.* [1] also reported a mean peak plasma level of cefotaxime at 0.5 h after intramuscular injection in goats. The $t_{1/2k_e}$ value of the present study was found to be higher ($1.03 \pm 0.02 \text{ h}$) than that of reported by Atef *et al.* [1] (39 min) in healthy goats which might be attributed to different climate and different varieties of goat. The lower body clearance (Cl_B) value might be the cause of persistent $t_{1/2k_e}$ in the present experiment. The $V_{d_{\text{area}}}$, V_{ss} and V_{d_c} values indicated wide distribution of cefotaxime after i.m. administration. The f_c and T~P values indicated shorter persistence of the drug in tissue compartment of normal

Table 1. Pharmacokinetic parameters of cefotaxime following single intramuscular administration at 50 mg/kg to normal and kidney damaged goats (n = 6, mean \pm SE)

Kinetic parameters	Normal goat	Kidney damaged goat
C_0 ($\mu\text{g/ml}$)	56.13 \pm 3.60	139.77 \pm 1.60**
ka (h^{-1})	4.51 \pm 0.27	1.46 \pm 0.03**
$t_{1/2,ka}$ (h)	0.16 \pm 0.01	0.48 \pm 0.01**
ke (h^{-1})	0.68 \pm 0.01	0.04 \pm 0.001**
$t_{1/2,ke}$ (h)	1.03 \pm 0.02	20.03 \pm 0.16**
k_{12} (h^{-1})	1.13 \pm 0.13	0.55 \pm 0.18**
k_{21} (h^{-1})	3.07 \pm 0.13	0.89 \pm 0.01**
k_{el} (h^{-1})	0.99 \pm 0.02	0.06 \pm 0.001**
Vd_c (L/kg)	0.92 \pm 0.06	0.36 \pm 0.004**
Vd_{area} (L/kg)	1.33 \pm 0.09	0.59 \pm 0.007**
V_{ss} (L/kg)	1.23 \pm 0.09	0.58 \pm 0.007**
AUC ($\mu\text{g. h/ml}$)	56.67 \pm 2.65	2440.10 \pm 24.26**
Cl_B (L/kg/h)	0.89 \pm 0.05	0.02 \pm 0.008**
f_c	0.69 \pm 0.01	0.60 \pm 0.003**
T~P	0.46 \pm 0.02	0.65 \pm 0.01**
F	0.88	0.79

**P < 0.01 compared to normal goat

Abbreviation: C_0 , zero time plasma drug concentration; ka, Absorption rate constant; $t_{1/2,ka}$, Biological half-life (Absorption phase); ke, Elimination rate constant; $t_{1/2,ke}$, Biological half-life (elimination phase); k_{12} , first order rate constant for transfer of drug from central compartment to peripheral compartment; k_{21} , First order rate constant for transfer of drug from peripheral to central compartment; k_{el} , First order elimination rate constant for disappearance of drug from the central compartment; Vd_c , Apparent volume of central compartment; Vd_{area} , Apparent volume of drug distribution; AUC, Total area under the concentration versus time curve; Cl_B , Total body clearance of a drug; f_c , Fraction of drug in the body that is contained in the central compartment; T~P, Tissue plasma ratio; F, Bioavailability.

goats.

The concentration of cefotaxime at 0.08 h was about two-fold higher, while body clearance value (Cl_B) was 44.5 times lower in kidney damaged than that of normal goats resulting into longer persistence of the compound in blood. Increases of BUN and creatinine level in blood suggest that uranyl nitrate damaged both Bowmans capsule and proximal convoluted tubules and in compliance cefotaxime excreted slowly from the body. Experimentally produced uremia coupled with elevation of BUN and creatinine levels induces progressive metabolic alkalosis and slow metabolism of drug [5,6]. Therefore, the low body clearance and prolonged blood disposition might be the sequelae of slow excretion of cefotaxime through kidney tubules and diminished metabolism of drug in kidney damaged goats. Besides, it is expected that the acidic drug like cefotaxime will remain maximally in ionized form during metabolic alkalosis and ionized drug molecules can not pass the biological membrane. Probably, these might have led to larger absorption half - life and limited or moderate distribution of drug in kidney damaged goats. Dutta *et al.* [2]) also reported previously that cefotaxime following intravenous administration in uranyl nitrate treated goats produced moderate distribution.

Bioavailability of cefotaxime in kidney damaged goats

was non-significantly lower than that of normal goats. This along with the long persistence of cefotaxime in blood in adequate concentration suggest that the frequency of dosing may be reduced in kidney damaged goats.

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