Effect of induced surgical stress and acute renal failure on disposition kinetics of ceftizoxime in goats

Ceftizoxime is a third generation cephalosporin used for the treatment of bacterial infections. Most of the cephalosporins are excreted by the kidney through glomerular filtration and tubular secretion. Renal impairment will result into a decreased renal clearance of these drugs. Therefore, acute renal failure may interfere with the excretion of these antibiotics resulting in alteration of their kinetics. Further some stressed conditions like surgical stress may alter the disposition kinetics of drugs. The present investigation was undertaken to study: (i) the disposition kinetics of ceftizoxime in goats with induced surgical stress and acute renal failure in comparison with normal goats, (ii) the other excretory pathway particularly through GI tract (Caecal pouch) and (iii) excretion of creatinine and BUN through GI tract to generate data in the selection of dosage regimen to treat surgical stress and acute renal failure cases.

Twelve clinically healthy adult black Bengal female goats (10–12 kg of 1–1.5 years age) were utilized in the experiment. They were fed with balanced feed and water ad libitum. They were divided into three groups. Group I healthy goat (HG) and II (ARF) consisted of three animals in each group, while group III consisted of six animals which was again subdivided into groups IIIA and IIIB (Surical Stress, SS).

In experiment 1, ceftizoxime (gift from Glaxo Smithkline Pharmaceuticals Ltd., Nashik, Maharashtra, India) was administered intravenously as a single dose (20 mg/kg) to group I(HG) goats and disposition kinetics and plasma protein binding studies were carried out. After one month interval of single intravenous administration the drug was administered by intramuscular route (thigh muscles) to the same group of goats. After i.v. and i.m. administrations blood samples were collected from the jugular vein at ‘0’ (before drug administration) and 0.08, 0.16, 0.33, 0.5, 0.66, 1, 2, 3, 4, 5, 6, 7, 8 and 10 h postdosing. Two millilitre of blood was collected at 0.25, 0.50, 0.75, 1.00, 1.25 and 1.45 h for estimation of ceftizoxime. Ceftizoxime was estimated in plasma/caecal content by the spectrophotometric method.[1,2]

In experiment 2, the animals were subdivided into groups IIIA and IIIB. The area of operative site of the animals was closely shaved and prepared aseptically. After 15 min of deep sedation with xylazine hydrochloride (1 mg/kg, i.m.) Lignocaine hydrochloride (2%) was infiltrated locally at operative site and the animal was kept in left lateral recumbency. A vertical incision of about 6 cm length was made on the hollow of the flank. The incision was extended by blunt dissection through the external and internal oblique and transverse abdominal muscles. The peritoneum was opened and the caecum was transected from colon near the ileocolic junction. With intact vascular supply the cut end of caecum was tethered to skin and caecostomy performed. The muscles and skin were closed in usual manner. Caecostomy was used for introduction and collection of normal saline with small opening while the colonic end of caecum was closed with suture. The operative site was flushed with normal saline solution followed by application of betadine ointment once daily for 5 days. Ceftizoxime was administered i.v., for disposition kinetics and plasma protein binding studies in goats of group III A, while the goats from group IIIB were administered i.m. ceftizoxime, only for disposition kinetics.

In experiment 3, acute renal failure was induced mechanically by blocking the urethra using Foley’s catheter. To ascertain the desired level of renal failure, blood urea nitrogen (BUN) and creatinine (CRT) levels were monitored.[3,4] The catheter was removed after 48 h following attainment of four times higher value of BUN and creatinine levels compared to normal one. Then ceftizoxime at 20 mg/kg was administered i.v. for plasma disposition kinetics and protein-binding studies.

Collection and processing of samples were performed as described earlier.

Caecal content (normal saline in caecal pouch) was collected at 0.25, 0.50, 0.75, 1.00, 1.25 and 1.45 h for estimation of ceftizoxime. Ceftizoxime was estimated in plasma/caecal content by the spectrophotometric method.[4]

Pharmacokinetic parameters of ceftizoxime were determined using a curve fitting software program (Pharmkit). Mean plasma concentration of ceftizoxime following single-dose intravenous administration in HG, SS and ARF has been plotted in Fig. 1. Maximum plasma concentrations of ceftizoxime were 78.85±8.74, 65.86±5.55 and 108.13±5.89 µg/ml in HG, SS and ARF goats respectively, while minimum concentrations for these goats were 2.56±0.68, 2.43±0.41 and 1.86±0.13 µg/ml, at 1, 8 and 12 h respectively.

Computerized semilogarithmic plot of plasma concentration of ceftizoxime against time showed “one-compartment open model” HG and ARF goats and “Two-compartment open model” for SS goats following intravenous administration (Fig. 1).

The β and t½ values for HG, SS, ARF goats were 3.73±0.36 h⁻¹ and 0.19±0.02 h; 0.26±0.06 h⁻¹ and 3.10±0.94 h; and 0.31±0.01 h⁻¹ and 2.17±0.08 h, respectively. The values of Vd and AUC were 0.21±0.03 l/kg and 26.70±3.39 µg h/ml for healthy, 0.65±0.03 l/kg and
105.00±16.25 µg h/ml for surgical stress, 0.28±0.02 l/kg and 217.31±6.96 µg h/ml for acute renal failure goats. On the other hand, the values of ClB were 0.75±0.09, 0.17±0.05 and 0.09±0.001 l/kg/h in healthy, surgically stressed and acute renal failure goats.

Maximum and minimum concentrations of ceftizoxime in HG and SS goats have been presented in Fig. 2 after i.m. administration.

The values of t½, Vd, and ClB were 1.64±0.01 and 2.58±0.34 h, 0.58±0.04 and 1.22±0.12 l/kg, 0.25±0.01 and 0.33±0.01 l/kg h in HG and SS goats after i.m. administration.

It is observed that adequate concentration of ceftizoxime in normal saline present in caecal pouch was achieved at 0.25 h (2.40±0.75 µg/ml), which was gradually increased till 1.75 h. The concentration of ceftizoxime was 35.70±1.07 mg/ml at 1.75 h.

The percentage of plasma protein bound ceftizoxime ranged from 32.05 to 53.20% at the drug concentration of 53.19±7.42 to 8.60±1.40 mg/ml in HG. Likewise, the plasma protein binding of ceftizoxime ranged from 35.28 to 52.23% at the drug concentrations of 42.23±9.27–15.60±2.09 mg/ml in SS goats. On the other hand, plasma protein binding of ceftizoxime ranged from 38.01 to 56.52 at the drug concentrations of 77.36±3.85–33.25±0.56 mg/ml in ARF goats.

Based on the pharmacokinetic parameters derived from the respective plasma concentration–time profile, rational dosage regimens for ceftizoxime for HG, SS and ARF have been formulated. It has been reported that most of the sensitive microorganisms are inhibited within the concentration range of 0.004–1.0 mg/ml. In view of this, it is advocated that the dose of ceftizoxime should be reduced and the dosing interval increased in surgical stress goats after i.m. administration.

The higher Ks and shorter t½ along with higher Clmax and shorter Tmax in healthy goats compared to surgical stress goats suggest rapid absorption of the drug within very short period in healthy animals after intramuscular administration. Stress induces complex biochemical mechanisms and produces generalized vasoconstriction, which may decrease the blood flow and in the process it may lead to slow absorption of drug from the site of administration by some unknown mechanism and therefore the blood flow to the intramuscular site will be restricted resulting in slow absorption of drug in goats with surgical stress group compared to the healthy group. Further, the concentration of ceftizoxime in caecal pouch may suggest that the transepithelial excretion of the drug through intestine.

Pharmacokinetic behaviour in HG and ARF goats follows ‘one-compartment model’. Further, ceftizoxime persisted till 1 h in HG and 12 h in ARF goats following intravenous administration. Besides, higher t½ and lower ClB values in ARF goats compared to HG suggest that ceftizoxime persisted in the body for a long time with lesser excretion.

The major excretory pathway of most of the cephalosporin derivatives is directed through the kidney particularly by glomerular filtration and active tubular secretion. The intensity of damage was established by estimating BUN and creatinine level in the blood. It was observed that the physical obstruction of urethra by Foley’s catheter caused significantly increased level of BUN and creatinine compared to control goats. Experimentally produced uremia is associated with an elevation of BUN and creatinine, progressive metabolic alkalosis and hypercapnia. The acute renal failure coupled with increased blood urea nitrogen might be responsible for slow excretion of ceftizoxime. Therefore, the lower total body clearance and prolonged ceftizoxime level in plasma were possibly due to lesser excretion through renal tubules compared to healthy goats.

The study suggests that ceftizoxime is capable of transmembrane excretion through GI tract. Accordingly the...
dose schedule of the drug during SS and ARF needs to be modified.

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