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Full Length Article

Comparative pharmacokinetics of cefoperazone following intravenous and intramuscular administration in goats

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Abstract The pharmacokinetic profile of cefoperazone was studied in goats following intravenous and intramuscular administration of 20 mg/kg body weight. Cefoperazone concentrations in serum were determined by microbiological assay technique using *Escherichia coli* (ATCC 10536) as test organism. Following i.v. administration, the cefoperazone serum concentration–time curve was best fitted in a two compartment open model. Cefoperazone has moderate distribution in the body of goats with Vd_{ss} of 0.44 ± 0.03 L/kg. The elimination half-life ($T_{0.5(\beta)}$), area under curve (AUC) and total body clearance (Cl_{tot}) were 1.97 ± 0.14 h, 149.63 ± 8.61 μg ml^{-1} h^{-1}, and 2.17 ml/min/kg, respectively. Following i.m. administration, the drug was very rapidly absorbed, with an absorption half-life ($T_{0.5(ab)}$) of 0.12 ± 0.01 h. The maximum serum concentration (C_{max}) of 30.42 ± 3.53 μg ml^{-1} was attained at (T_{max}) 0.58 ± 0.02 h, with an elimination half-life ($T_{0.5(el)}$) of 2.53 ± 0.11 h. The systemic bioavailability of cefoperazone in the goats after i.m. administration was 83.62% and *in vitro* protein binding was 20.34%. The serum concentrations of cefoperazone along 12 h post i.m. injection in this study were exceeding the MIC of different susceptible microorganisms responsible for serious disease problems. Consequently, a suitable intramuscular dosage regimen for cefoperazone was 20 mg/kg repeated at 12 h intervals in goats. The drug was detected in urine up to 12 and 18 h following i.v. and i.m. administration, respectively.

1. Introduction

Cefoperazone is a semi-synthetic third generation, piperazine β-lactam antibiotics that possesses broad spectrum activity against aerobic and anaerobic gram-positive and gram-negative bacteria [1]. Cefoperazone is used in the treatment

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of bone and joint infections of horses [2], calf diseases such as diarrhea and pneumonia [3] and has good penetration into the pancreas indicating its usefulness for the prophylaxis and therapy of secondary pancreatic infections [4]. Only a few cephalosporins have a high biliary excretion, cefoperazone being one of them. Cefoperazone exhibits a longer half-life of elimination than older members of the group [5] and good penetration into organic bone [6]. The pharmacokinetics of cefoperazone had been investigated in a number of animal species including unweaned calves [7], horse [8], dog [9], buffalo calves [10,11], cross bred calves [12,13] and sheep [14]. The aim of the study was to determine the pharmacokinetic parameters of cefoperazone following a single intravenous and intramuscular administration at the dose of 20 mg/kg b.wt. in goats.

2. Materials and methods

2.1. Drugs and chemicals

Cefoperazone sodium powder (CEFOBID®, produced by Smithkline Beecham Egypt LLc for Pfizer Egypt) was diluted with sterile water just prior to administration. Mueller–Hinton agar was purchased from Mast Group Ltd., Merseyside, UK.

2.2. Animals

Ten clinically normal goats were used in this investigation. The body weight and age ranged from 23 to 31 kg and from 2 to 3 years old, respectively. Animals were housed in hygienic stable, fed on barseem, drawa and concentrate. Water was provided *ad libitum*. None of the animals were treated with antibiotics for one month prior to the trial.

2.2.1. Experimental design

The study was performed in two phases, following a crossover design (2 × 2) with a 15-day washout period between the two phases. Five animals were given a single i.v. injection into the left jugular vein at a dose of 20 mg/kg body weight (b.wt.) cefoperazone, and the other five were injected i.m. into the gluteal muscle with the drug at the same dose. Five milliliter venous whole blood samples were taken. The sampling times were 0.08, 0.166, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 h after treatment. Blood samples were left to clot; the clear sera were separated by centrifugation at 3000 r.p.m for 15 min and stored at −20 °C until assayed. After washout period of 15 days, the animals that had been injected i.v. with the drug were injected i.m. and vice versa. Blood was collected and processed as above. Goats were catheterized with an indwelling balloon catheter (Foley Urinary Catheter, No. 12, Timedco, Atlanta, GA, USA). 5 ml urine samples were collected at 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 h after administration of the drug. The samples stored at −20 °C until assayed.

2.2.2. Drug bioassay

Concentrations of cefoperazone in samples were determined by the microbiological assay method described by [15] using *Escherichia coli* (ATCC 10536) as test organism [13]. This method estimated the level of drug having antibacterial activity, without differentiating between the parent drug and its active metabolites. The application of microbiological assay for measuring cefoperazone concentration is suitable [13]. Six wells were made at equal distances in standard petri-dishes containing 25 ml seeded agar. The wells were filled with 100 μl of either the test samples or the cefoperazone standard concentrations. The plates were kept at room temperature for 2 h before being incubated at 37 °C for 18 h. Zones of inhibition were measured using micrometers and the cefoperazone concentrations in the test samples were calculated from the standard curve. Cefoperazone standard solution of concentrations of 0.5–100 μg/ml were prepared in antibiotic-free goats serum and phosphate buffer saline. Standard curves of cefoperazone were prepared in antibacterial-free goat serum by the appropriate serial dilution. The standard curve in goat serum was linear over the range from 0.5 to 100 μg/ml and the value of correlation coefficient (r) was 0.991. The limit of quantification was 0.5 μg/ml. Protein binding of cefoperazone was estimated according to [16].

2.3. Pharmacokinetic analysis

A pharmacokinetic computer program (R-strip, Micro-math, Scientific software, USA) was used to analyse the concentration–time curves for each individual animal after the administration of cefoperazone by different routes. Following i.v. and i.m. administrations, the appropriate pharmacokinetic model was determined by visual examination of individual concentration–time curves and by application of Akaike's information criterion (AIC) [17]. The pharmacokinetic parameters were reported as mean ± SE. All statistical analysis was carried out according to [18].

3. Results

Mean serum concentrations of cefoperazone in goats following i.v. and i.m. administrations of 20 mg/kg are summarized in (Fig. 1). These data are best fitted to a two-compartment open model and the drug was detected in serum up to 8 and 12 h following i.v. and i.m. administration, respectively. The pharmacokinetic parameters of cefoperazone in goats following i.v. and i.m. administration of 20 mg/kg are summarized in (Tables 1 and 2). Following i.v. administration, cefoperazone has moderate distribution in the body of goats with Vd_{ss} of 0.44 ± 0.03 L/kg. Cefoperazone was rapidly eliminated ($T_{0.5(\beta)}$: 1.97 ± 0.14 h) from the body. Following i.m. administration, the drug was very rapidly absorbed with a short absorption half life $T_{0.5(ab)}$ of 0.12 ± 0.01 h. The mean peak serum concentration (C_{max}) was 30.42 ± 3.53 μg ml^{-1} achieved at (T_{max}) 0.58 ± 0.02 h. The systemic bioavailability of cefoperazone in the goats after i.m. administration was 83.62%. *In vitro* protein binding was 20.34%. Mean urine concentrations of cefoperazone in goats following i.v. and i.m. administration of 20 mg/kg are summarized in (Fig. 2).

4. Discussion

Following i.v. administration of cefoperazone in goats at a dose of 20 mg/kg, no adverse effects or toxic manifestation was observed. The results revealed that serum cefoperazone concentration versus time decreased in a bi-exponential manner, demonstrating the presence of distribution and elimination phases and justifying the use of two-compartment open model. This finding is in agreement with cefoperazone in horse [8], in