International Journal of Veterinary Science and Medicine

ISSN: (Print) 2314-4599 (Online) Journal homepage: https://www.tandfonline.com/loi/tvsm20

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To cite this article: Taha Attia, Ashraf El-Komy, Mohamed El-Hewaity, Amera Abd El Latif & Saber El-Hanbally (2015) Comparative pharmacokinetics of cefoperazone following intravenous and intramuscular administration in goats, International Journal of Veterinary Science and Medicine, 3:1-2, 21-25, DOI: 10.1016/j.ijvsm.2015.08.002

To link to this article: https://doi.org/10.1016/j.ijvsm.2015.08.002

International Journal of Veterinary Science and Medicine (2015) 3, 21–25

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Comparative pharmacokinetics of cefoperazone following intravenous and intramuscular administration in goats

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Received 26 January 2015; accepted 11 August 2015
Available online 31 October 2015

KEYWORDS

Cefoperazone;
Kinetic;
Goat

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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Peer review under responsibility of Faculty of Veterinary Medicine, Cairo University.

http://dx.doi.org/10.1016/j.ijvsm.2015.08.002

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

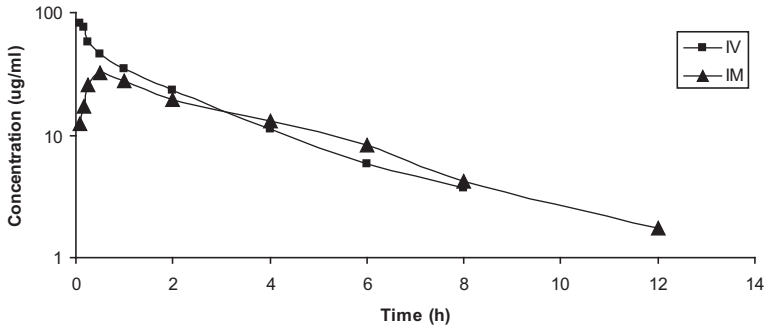

Fig. 1 Semi-logarithmic graph depicting the time-concentrations course of cefoperazone in serum of goats (n = 10) following a single intravenous and intramuscular administration of 20 mg/kg body weight.

Table 1 Mean (±SE) kinetic parameters of cefoperazone (20 mg/kg) following a single intravenous injection in goats (n = 10).

Parameter	Unit	Mean (±SE)
Cp°	μg ml^{-1}	102.31 ± 7.22
A	μg ml^{-1}	54.10 ± 4.38
α	h^{-1}	4.59 ± 0.31
$T_{0.5(\alpha)}$	h	0.15 ± 0.002
Vc	L kg^{-1}	0.20 ± 0.005
Vd_{area}	L kg^{-1}	0.38 ± 0.02
Vd_{ss}	L kg^{-1}	0.44 ± 0.03
$Vd_{(B)}$	L kg^{-1}	0.41 ± 0.01
K_{12}	h^{-1}	2.59 ± 0.04
K_{21}	h^{-1}	2.15 ± 0.04
K_{el}	h^{-1}	0.75 ± 0.05
B	μg ml^{-1}	48.20 ± 3.89
β	h^{-1}	0.35 ± 0.005
$T_{0.5(\beta)}$	h	1.97 ± 0.14
AUC	μg ml^{-1} h^{-1}	149.63 ± 8.61
MRT	h	2.15 ± 0.12
Cl_{tot}	ml/min/kg	2.17 ± 0.10

Cp°: Concentration at zero-time; A and B: Zero-time intercepts of the biphasic disposition curve; α and β: Hybrid rate constants representing the slopes of distribution and elimination phases, respectively; K_{12}: First-order constant for transfer from central to peripheral compartment; K_{21}: First-order constant for transfer from peripheral to central compartment; K_{el}: Elimination rate constant; $T_{0.5(\alpha)}$: Distribution half-life; $T_{0.5(\beta)}$: Elimination half-life; $AUC_{(0-inf)}$: Area under serum concentration–time curve; MRT: Mean residence time; Vc: Apparent volume of central compartment; Vd_{area}: Apparent volume of distribution calculated by area method; Vd_{ss}: Volume of distribution at steady state: $Vd_{(B)}$: Apparent volume of distribution calculated by extrapolation method; Cl_{tot}: Total body clearance.

dog [9] and in cross bred calves [12]. The drug was rapidly distributed with a short $T_{0.5(\alpha)}$: 0.15 h. This value was close to those reported in calves $T_{0.5(\alpha)}$: 0.15 h [19] and dog $T_{0.5(\alpha)}$: 0.20 h [9], shorter than those reported in sheep $T_{0.5(\alpha)}$: 0.53 h [14].

The elimination half-life and MRT were 1.97 and 2.15 h, respectively, the results were near to those reported in cross bred calves 2.05 and 2.28 h, respectively [12] and in dog 1.40 and 1.55 h, respectively [9], shorter than those reported in sheep 3.80 and 3.29 h, respectively [14]. The value of Vd_{ss} (0.44 L/kg) indicated moderate extravascular distribution of the drug. This value was close to those reported in sheep Vd_{ss}: 0.51 L/kg [14]. The total body clearance of cefoperazone following i.v. administration was 2.17 ml/min/kg. The value was close to those reported in dog 1.96 ml/min/kg. [9], while it is slower than 5.16 ml/min/kg reported in sheep [14], 8.16 ml/min/kg reported in unweaned calves [7] and 11.50 ml/min/kg reported in cross bred calves [12].

Following i.m. administration of cefoperazone in goats at a dose of 20 mg/kg, the drug was very rapidly absorbed with a short absorption half life $T_{0.5(ab)}$ of 0.12 h. This value was shorter than those reported in dog 0.48 h [9]. The maximum serum concentration (C_{max}) of 30.42 μg ml^{-1} was attained at (T_{max}) 0.58 h post administration. However, lower value of C_{max} like 25.67 μg ml^{-1} at 0.5 h in sheep [14], 24.5 μg ml^{-1} at 1.5 h in dog [9] and 9.76 μg ml^{-1} at 0.75 h in cross bred calves [13] had been reported.

The elimination half-life of cefoperazone following i.m. administration was 2.53 h. This value was close to those reported in unweaned calves 2.28 h [7], dog 2.24 h [9] and cross bred calves 2.31 h [13]. While it is shorter than value reported in sheep 3.32 h [14]. The mean residence time (MRT) was 3.34 h. This value was similar to those reported in cross bred calves 3.62 h [13]. However it is shorter than value reported in sheep 4.27 h [14] and dog 4.05 h [9], but longer than value recorded in unweaned calves 2.34 h [7].

Table 2 Mean (±SE) kinetic parameters of cefoperazone (20 mg/kg) following a single intramuscular injection in goats (n = 10).

Parameter	Unit	Mean (±SE)
A	μg ml^{-1}	30.83 ± 4.32
K_{ab}	h^{-1}	5.64 ± 0.41
$T_{0.5(ab)}$	h	0.12 ± 0.01
B	μg ml^{-1}	37.32 ± 5.88
K_{el}	h^{-1}	0.27 ± 0.02
$T_{0.5(el)}$	h	2.53 ± 0.11
C_{max}	μg ml^{-1}	30.42 ± 3.53
T_{max}	h	0.58 ± 0.02
AUC	μg h ml^{-1}	125.12 ± 8.89
MRT	h	3.34 ± 0.23

A: Zero-time intercept of distribution phase; K_{ab}: First-order absorption rate constant; $T_{0.5(ab)}$: Absorption half-life; B: Zero-time intercept of elimination phase; K_{el}: First-order elimination rate constant; $T_{0.5(el)}$: Elimination half-life; C_{max}: Maximum serum concentration; T_{max}: Time to peak serum concentration; $AUC_{(0-inf)}$: Area under serum concentration–time curve; MRT: Mean residence time.

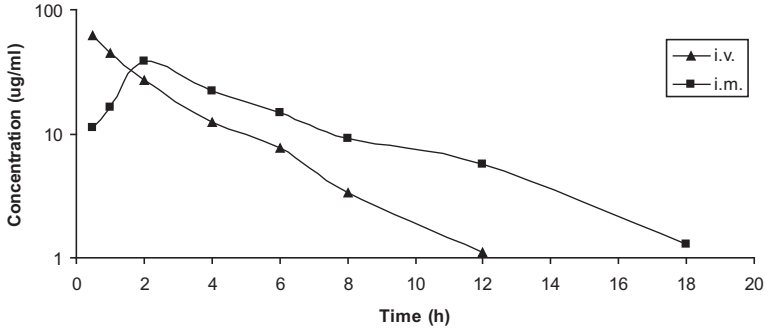

Fig. 2 Semi-logarithmic graph depicting the time-concentrations course of cefoperazone in urine of goats ($n = 10$) following a single intravenous and intramuscular administration of 20 mg/kg body weight.

The value of systemic bioavailability (83.62%) indicated good absorption of cefoperazone from i.m. injection site. This value was higher than those reported in unweaned calves 76.3% [7] and sheep 71.83% [14]. While this value was close to those reported for cefepime in goats 86.45% [20] and ewes 86.8% [21]. High bioavailability of cefoperazone and maintenance of therapeutic concentration up to 12 h after i.m. administration suggests that the drug is suitable for i.m. administration for the treatment of systemic bacterial infections in goats. *In vitro* protein binding was 20.34%, compared with 24.9% reported in cross bred calves [13].

The serum level of $\geqslant 0.2\ \mu g\ ml^{-1}$ for third generation cephalosporin is considered adequate against most sensitive bacteria, including *Enterobacteriaceae* Spp. [22]. However, a serum concentration of 0.25–2.0 $\mu g\ ml^{-1}$ has been reported as MIC_{90} of cephalosporin against animal pathogens [23]. In the present study an average value of MIC (1.0 $\mu g\ ml^{-1}$) has been taken into consideration. The drug was detected above MIC in serum up to 8 and 12 h following i.v. and i.m. administration, respectively.

Cefoperazone was detected in urine at high concentrations following i.v and i.m. administration for 12 and 18 h, respectively. The detected concentrations of the drug in urine exceed the MIC_{90} for all bacterial pathogens responsible for urinary tract infections in goats. The result suggests the possibility of using cefoperazone in treatment of such disease conditions in goats.

5. Conclusion

A cefoperazone dose of 20 mg/kg is sufficient to maintain serum concentration of the drug above the MIC_{90} when it is administered at 8 and 12 h interval following intravenous and intramuscular administration, respectively. Consequently, cefoperazone can be used safely and effectively for treat the infections in goats.

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