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PHARMACOKINETICS AND CLINICAL EFFICACY OF CEFOTAXIME FOR THE TREATMENT OF SEPTICAEMIA IN DOGS

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Considering the already known pharmacological features of cefotaxime, a study with two approaches of pharmacokinetics and clinical efficacy in septicaemic dogs was carried out. Pharmacokinetic variables were defined for doses of 10 mg/kg, and 20 mg/kg, utilising a quantitative bacteriological analysis. Values for half-life ($T_{½\beta}$) at 10 mg/kg were 0.8, 1.48 and 1.52 h for the i.v., s.c. and i.m. routes, respectively. Corresponding values for the 20 mg/kg dose for the same routes were 0.8, 1.49 and 1.53 h, respectively. Relatively fast clearance (ranging from 0.58 to 0.64 L/kg/h) allowed a maximum dose interval of 12 h. The above-stated doses of cefotaxime were administered i.v. to 40 cases of septicaemia, clinically divided into 20 moderately severe cases treated with 10 mg/kg i.v., of cefotaxime *bid*, and 20 severe ones, treated with 20 mg/kg i.v. of cefotaxime *bid*. Injections continued until a previously defined criterion of 'clinically recovered' was obtained. Thereafter, a follow-up treatment was established using the same dose and dose-interval but through the s.c. route. Due to the apparent volumes of distribution obtained (ranging from 0.48 to 0.51 L/kg), considering the overall clinical efficacy obtained (90% for the 10 mg/kg dose and 75% for the 20 mg/kg dose), and due to the rapid improvement observed after a few doses of the drug (1.8 to 2.5 doses to 'clinical improvement'), it is safe to postulate such doses of cefotaxime as excellent choices for the treatment of septicaemia in dogs.

Key words: Cefotaxime, dogs, pharmacokinetics, septicaemia, efficacy

In dogs, septicaemia is confronted with relative frequency in clinical settings, often as a sequel to postoperative infections, following both soft tissue and orthopaedic surgery. It is also encountered during septicaemic phases of pyometra, following complications of respiratory infections (Nostrandt, 1990), in untreated or poorly treated urinary infections (Teshager et al., 2000), in cases of social neglect with concurrent malnutrition and lack of hygiene (Nostrandt, 1990), or even as a result of tooth extraction (Withrow, 1997).

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In practice, diagnosis is based upon background and clinical signs, taking into account characteristics of the primary infection. Clinical signs are ambiguous, but taken together, suffice to reach a diagnosis. For example, weak and fast pulse, pale and mottled mucous membranes, partial or total loss of consciousness, fever in some cases and, occasionally, seizures in severe cases. Various bacteria have been identified, including *Staphylococcus aureus, S. intermedius, Pasteurella canis, Streptococcus canis,* group G streptococci, *Actinomyces* sp., *Pseudomonas aeruginosa, Proteus mirabillis,* indole-positive *Corynebacterium* sp*., Escherichia coli* and even *Bordetella bronchiseptica* (Nostrandt, 1990). Antibiotics of choice are those having a low volume of distribution, usually less than 0.5 L/kg, that can cause quick bacterial destruction. Among these, aminoglycosides, in particular gentamicin and amikacin, the β-lactams and a combination of both, are preferred (Sumano and Borbolla, 1996). Given that most of these patients show diverse levels of renal failure, it is not always easy to adjust the aminoglycoside dose without risking further renal damage (Diaz et al., 1995; Sumano and Brumbaugh, 1995). The third-generation cephalosporins, in particular cefotaxime, could potentially be used to treat septicaemia in small animal species. These antibacterial drugs possess considerable potency against Gram-positive and negative, aerobic and anaerobic bacteria. In species other than dogs, cefotaxime has shown better tissue distribution compared to other β-lactam molecules, reaching therapeutic concentrations even in cerebrospinal fluid (0.14 to 1.81 μg/ml) (Nau et al., 1993), while maintaining a useful plasma concentration for cases involving septicaemia. Furthermore, plasma protein binding of cefotaxime in dogs is relatively small (approximately 50%); thus, the drug is capable of having a rapid onset of activity (Fernandez et al., 1991). Its toxicity in many species, including dogs, is low (LD_{50} 7000 mg/kg) (Nakano et al., 1989; Ziv et al., 1996), which is much better than that exhibited by aminoglycosides (Sumano and Brumbaugh, 1995; Sumano et al., 2000). Due to its efficacy and low risk, it has been successfully used in various types of septicaemia, such as neonatal foal septicaemia with meningitis (Morris et al., 1987), human neonatal septicaemia with secondary complications (Billiet et al., 1989), pancreatitis-associated septicaemia in man (Trudel et al., 1994), and in multiple protocols which require a mix of rapid onset of antibacterial activity and a good balance between tissue distribution and plasma permanence. In the dog, elimination of cefotaxime C^{14} is known to occur mainly by renal excretion (80%), with 20 to 32% not biotransformed (MacDonald et al., 1984).

Usually, cefotaxime is used at a dose of 50 mg/kg in man (Bocazzi et al., 1998). However, some trials in veterinary medicine have used a dose of 10 mg/kg, *i.e.,* in calves and goats (Sharma et al., 1995). It is quite possible that the reasoning behind this dose is a slower renal clearance (Navasa et al., 1996), or the drug could be used feasibly when pathogen sensitivity is high, as has been shown when using cefotaxime in children with pneumonia (Turnidge, 1995). In one study, a dose of

33.3 mg/kg proved to be more efficient than 50 mg/kg for the treatment of paediatric patients having respiratory difficulties (Bocazzi et al., 1998).

Notwithstanding the apparent benefit to be obtained by using cefotaxime in the small animal clinic, its pharmacokinetics at the 10 and 20 mg/kg dose level in diseased animals have not been determined, nor have data concerning its use in cases of septicaemia been found. Therefore, the aim of the present work was to carry out a pharmacokinetic study in cases of septicaemia, followed by a clinical evaluation of the aforementioned doses.

Materials and methods

Pharmacokinetic phase

Twelve clinically healthy mixed-breed male and female dogs, averaging 12 kg weight and with ages ranging from eight months to seven years, were included in this phase. Animals had not been medicated with antibacterial drugs for many months. Animals were housed in individual sheltered kennels with a mean environmental temperature of 20 °C and received commercially available food and water *ad libitum*. Six dogs were assigned, at random, to each of the two dose regimens (10 and 20 mg/kg) and all were tested using the three application routes: i.v., i.m. (semitendinous muscle) and s.c. (dorsal portion of the neck scruff), allowing at least one week of product elimination between tests. Commercially available powdered cefotaxime was reconstituted for use as per manufacturer's instructions[**]. Bolus doses were administered and then blood samples were taken by venipuncture using heparin vacutainers at times 10, 15 and 45 min, as well as 1, 1.5, 3, 5, 7, 9 and 12 h. Samples were immediately centrifuged (3000 *g*/10 min), plasma separated and frozen at –20 °C for no longer than five days prior to analysis. The activity/concentration compounded values for cefotaxime and its possible metabolites were determined using the technique of Bennet et al. (1966), based on the agar diffusion of the drug in Mueller-Hinton media and utilising *Escherichia coli* ATCC 10536 as the reference bacteria, with canine plasma as diluent. Lower limit of detection was 0.1 μg/ml and regression values showed an *r* value of 0.98. Data for activity/concentration *vs.* time were processed using the PKAnalyst[***] pharmacokinetic software package using model 7 for the i.v. route and model 14 for the i.m. and s.c. routes with the following general formulas:

Model 7: $\text{Concentration (time)} = Ae^{-\alpha \cdot \text{Time}} + Be^{-\beta \cdot \text{Time}}$

Model 14: $\text{Concentration (time)} = Ae^{-\alpha \cdot (\text{Time} - \text{T latency})} + Be^{-\beta \cdot (\text{Time} - \text{T latency})} + Ce^{-KA1}$

[**]Zeefotax, Cpmax Pharmaceuticals, Mexico City
[***]MicroMath Sci., Salt Lake City, Utah, 1996

Variables determined were: T½β = half-life of the elimination phase; T½ab = half-life of the absorption phase; AUC = area under the time *vs.* concentration curve; Cp_{max} = maximum serum concentration; T_{max} = time for Cp_{max}; β = hybrid constant of elimination following Cp_{max} or the post-distribution phase; Vd_{AUC} = apparent volume of distribution area for the i.v. route or using the post-distribution phase extrapolated to the 'Y' axis for the i.m. and s.c. routes; Cl_s = systemic clearance; F = bioavailability; Vd_c = apparent volume of distribution for the central compartment; C_{po} = plasma concentration at time zero. Calculations were based on formulas proposed by Riviere (1999). Statistical analysis for these data was carried out using a random effects analysis of variance while comparison between means was done using the Bonferroni '*t*' test[****].

Clinical phase

Animals in this trial were clinically diagnosed as septicaemic, according to the inclusion criteria described in Table 1. Two groups with 20 animals each were included in this study. Those classified as moderately severe (Sep-A), satisfying six or less of the clinical signs listed in Table 1, were treated with a 10 mg/kg i.v. dose of cefotaxime *bid*. Those classified as severe (Sep-B), satisfying more than six of the clinical signs listed in Table 1, were treated with a 20 mg/kg i.v. dose of cefotaxime *bid*. Prior to treatment, blood samples were obtained and sent to the laboratory for blood culture and causative agent identification, as per usual practice. The first isolation was carried out in blood agar, upon which the usual biochemical tests were performed (Quinn, 1994). Intravenous treatments with cefotaxime were continued until a clinical recovery from septicaemia was obtained. Clinical recovery criterion was based upon absence of clinical signs listed in Table 1, return of voluntary food and water intake, and apparently normal urine production visually assessed as being close to 10 to 20 ml/kg/day. In addition, supportive therapy was instituted in all cases, consisting of 40 ml/kg/h of physiological saline solution for 4 h, followed by 10 ml/kg/h until normal food and water intake returned. Also, dexamethasone sodium phosphate injection (Decadron®) was applied at a dose of 0.5 mg/kg *sid* for a total of three doses.

It is important to emphasise that once 'clinical recovery' was established, treatment was continued with the same drug, at the same dose rates but using a s.c. route, and for a sufficient amount of time as to reach complete clinical recovery as assessed by absence of clinical signs and resolution of the underlying problem. This latter phase was carried out at the pet's premises, supervising obvious good animal welfare conditions.

The probable causes of septicaemia and the bacteria considered to be causative agents as derived from blood cultures, were noted in all cases. The

[****]JMP, SAS Company, 1996

following variables were evaluated: number of doses needed to observe clinical improvement (decrease of at least two of the clinical signs from Table 1), number of doses needed to observe clinical recovery (absence of clinical signs), number of cured/dead, and number of patients transferred to a different therapeutic protocol when no improvement was noted. To evaluate if there were differences in clinical efficiency between the two doses used, Ji^2 and *Kappa* analyses were carried out.

Results

The qualitative/quantitative analytic technique used showed a 92% plasma recovery and an intra-assay error not greater than 5%. Table 2 presents data corresponding to the pharmacokinetics obtained for cefotaxime. Statistical analysis demonstrated, for almost all variables obtained, no significant differences between i.m. and s.c. groups, nor between the two different doses assessed. However, these routes showed some statistically significant differences with the i.v. route ($P < 0.05$) for both dose levels, but not between different doses through the i.v. route. Mean activity/concentration values *vs.* time for the three routes and the two dose regimes used, are presented in Fig. 1. Table 3 summarises efficacy for the two doses used for the treatment of septicaemia. The efficacy of the two doses compared was not statistically different ($P < 0.05$). *Kappa* statistical analysis reflects the almost perfect concordance of values for both doses. Causative agents identified are listed in Table 3.

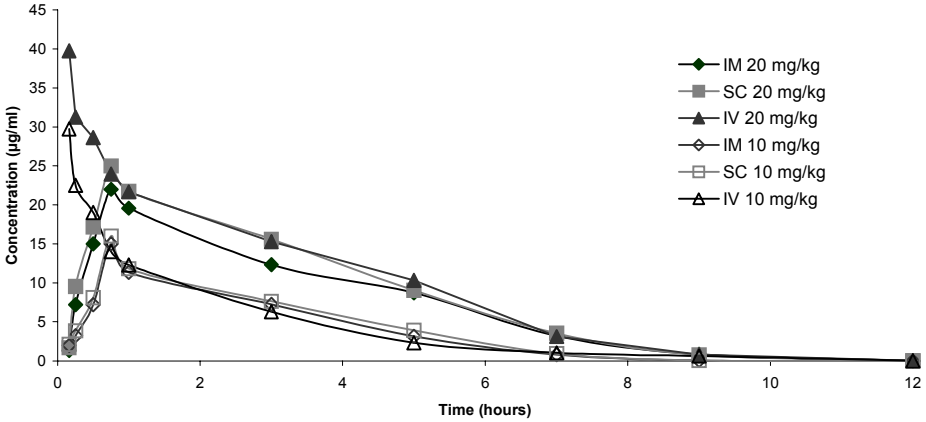

Fig. 1. Compounded plasma activity/concentration *vs*. time profiles for sodium cefotaxime and its metabolites following bolus doses of 10 mg/kg and 20 mg/kg of the antibacterial, via intravenous (i.v.), intramuscular (i.m.) and subcutaneous (s.c.) routes

Table 1: Inclusion criteria for dogs with two severity levels of septicaemia. Group distribution depended on: Sep-A (moderately severe) if patient met 6 or less of the listed signs. This group was treated with 10 mg/kg *bid* of sodium cefotaxime (Zeefotax®) and Group Sep-B (severe) with more than 6 clinical signs and they were treated with 20 mg/kg *bid* of sodium cefotaxime (Zeefotax®)

Clinical signs		Group	
		Sep-A	Sep-B
Pulse rate		Tachycardia (160–180), strong pulse	Tachycardia (160–180), thready pulse
Respiratory rate		Tachypnoea (30–40)	Cheyne-Stokes or Kussmaul
Oral mucosa		Congestion and moderate petechiae	Congestion and marked petechiae
Fever		Elevated (40 °C or more)	Absent
CNS:	Consciousness	Partially conscious, disoriented	Total or almost total unconsciousness
	Convulsions	Slight or absent	Evident
Eyes:	Pupillary reflexes	Slow	Absent
	Pupil	Normal or miotic	Dilated

Table 2: Mean ± SD of pharmacokinetic variables obtained for sodium cefotaxime (Zeefotax®) at the 10 mg/kg and 20 mg/kg doses, for i.v., i.m. and s.c. routes. Calculated from ANOVA and Bonferroni tests, $P > 0.05$. Statistically significant differences are shown with different letters per column

Group	T½β (hrs)	T½ab (hrs)	AUC (µg/ml/hr)	Cpmax (µg/ml)	Tmax (hrs)	Cls (L/kg/hr)	Vdc (L)	β (hr-1)	Cpo µg/ml	VdAUC (L/kg)	F (%)
Dose: 10 mg/kg											
i.v.	0.8 ± 0.02^{a}	–	48.21 ± 3.21^{a}	–	–	0.63 ± 0.05^{a}	2.25 ± 0.64^{a}	1.91 ± 0.42^{a}	28.21 ± 3.21^{a}	0.38 ± 0.06^{a}	–
s.c.	1.48 ± 0.35^{b}	0.42 ± 0.035^{a}	45.18 ± 2.98^{a}	15 ± 3.91^{a}	0.45^{a}	0.58 ± 0.07^{a}	–	1.29 ± 0.35^{b}	–	0.35 ± 0.05^{ab}	93.71 ± 2.21^{a}
i.m.	1.52 ± 0.32^{b}	0.36 ± 0.05^{b}	41.48 ± 3.65^{a}	16 ± 3.42^{a}	0.45^{a}	0.64 ± 0.05^{a}	–	1.79 ± 0.36^{ab}	–	0.33 ± 0.06^{b}	86.04 ± 3.54^{b}
Dose: 20 mg/kg											
i.v.	0.8 ± 0.02^{a}	–	104.16 ± 5.32^{b}	–	0.45^{a}	0.64 ± 0.07^{a}	2.51 ± 0.71^{a}	1.89 ± 0.59^{ab}	40.32 ± 2.6^{b}	0.39 ± 0.08^{b}	–
s.c.	1.49 ± 0.42^{b}	0.38 ± 0.04^{ab}	95.09 ± 8.36^{c}	22 ± 3.53^{b}	0.45^{a}	0.62 ± 0.07^{a}	–	1.56 ± 0.38^{b}	–	0.34 ± 0.04^{ab}	91.29 ± 3.94^{a}
i.m.	1.53 ± 0.45^{b}	0.39 ± 0.06^{ab}	83.27 ± 9.32^{d}	25 ± 3.62^{b}	0.45^{a}	0.61 ± 0.06^{a}	–	1.34 ± 0.65^{b}	–	0.35 ± 0.05^{ab}	79.94 ± 5.65^{c}

N = 6 dogs per route of administration; T½β = half-life of the elimination phase; T½ab = half-life of the absorption phase; AUC = area under the time *vs.* activity/concentration curve; Cpmax = maximum plasma concentration; Tmax = time for Cpmax; β = hybrid constant of elimination following Cpmax or the post-distribution phase; Vdauc = using Cpo as the post-distribution phase extrapolated to the 'Y' axis after the s.c. and i.m. injections; Cls = systemic clearance; F = bioavailability; Vdc = apparent volume of distribution of the central compartment; Cpo = plasma concentration at time zero

Table 3

Cases of septicaemia treated in dogs and clinical efficacy of supportive therapy and cefotaxime (Zeefotax®) sodium administration at a 10 mg/kg (Sep-A) and 20 mg/kg (Sep-B) dose. Using Ji2 ($P > 0.05$) and Kappa analyses

Group	Sep-A*	Sep-B*
Cases	12 lesions 3 neglect/malnutrition 3 pyometra 2 intestinal obstructions	8 lesions 3 necrotic mastitis 4 urinary tract infections 2 gunshot peritonitis 1 gingivitis/alveolitis
Mean dose number to attain recovery	4	2
Treated/cured/dead/change of treatment regimen	20/18/1/1	20/15/4/1
Mean dose number to attain clinical improvement	6	3
Causative agents isolated	*4 Staphylococcus aereus* 2 *S. intermedius* *2 Pasteurella canis* *3 Streptococcus canis* *1* group G *Streptococcus* *2 Actinomyces* sp. 3 *Pseudomonas aeruginosa* *1 Proteus mirabillis* 1 *Corynebacterium* sp. *6 Escherichia coli, Bordetella bronchiseptica*	*6 Staphylococcus aereus* 2 *S. intermedius* *4 Pasteurella canis* *3 Streptococcus canis* *1* group G *Streptococcus* *1 Actinomyces* sp. *4 Pseudomona aeruginosa* *3 Proteus mirabillis* 1 *Proteus* indole + 4 *Corynebacterium* sp. *6 Escherichia coli* 2 *Bordetella bronchiseptica*

*See Table 1 for Sep-A and Sep-B classification

Discussion

Considering that cefotaxime may have a sufficiently long and potent postantibiotic effect (Rubinstein and Lang, 1992), and given its T½β values (i.v. = 0.8 h; i.m. and s.c. = 1.5 h), it would be reasonably safe to propose that cefotaxime should be administered at least *tid* in the case of i.v. administration and *bid* or *tid* in the case of i.m. and s.c. administration. In contrast, i.m. or s.c. injection of this drug may last longer within the body due to a slower clearance, but with a shorter Cpmax value. It can then be argued that a dose interval extension to 12 h when using the i.v. route could only be based upon a postantibiotic effect, a feature thought to prolong the antibacterial action of β-lactam antibacterial agents (Rubinstein and Lang, 1992; Wang et al., 1998). Nevertheless, given the low toxicity exhibited by cefotaxime and the life-threatening nature of septicaemic conditions, a more aggressive approach to control septicaemia should be proposed, hence an eight-hour or less dose-interval should be imposed (Sumano and Borbolla, 1986). Volumes of distribution were Vd_c = 2.25 L and Vd_{AUC} = 0.40 L/kg, which would be considered to be among the highest for a β-lactam drug (Riviere, 1999; Sumano and Ocampo, 1987) but at the same time sufficient for the treatment of septicaemia, while most likely achieving therapeutic tissue concentrations (Nostrandt, 1990; Bocazzi et al., 1998).

The pharmacokinetics of third-generation cephalosporin derivatives has not been extensively studied in dogs. The latest of the third-generation cephalosporins studied in dogs was cefepime. This agent given at 14 mg/kg showed lower Vdauc values than the corresponding value for cefotaxime in this work (Gardner and Papich, 2001). Also, faster clearance of cefepime as compared with cefotaxime made these authors suggest a dose interval of only 6 h and, because cefepime appears to be less potent than cefotaxime (Lavy et al., 1995), a high dose of 40 mg/kg was recommended. Cefoxitine and cefotetan are cleared from the body at approximately the same rate as cefotaxime, particularly after its subcutaneous injection. However, cefoxitine and cefotetan showed considerably lower apparent volume of distribution values and a dose of 30 mg/kg every 8 hours was proposed for cefotetan (Petersen and Rosin, 1993). As in this study for cefotaxime, cephalosporins seem to be rapidly cleared in dogs. Carli et al. (1999) suggested a dose interval of 6 to 8 h for cephalexin after i.m. administration, but much faster elimination rates have been found (Schermerhorn et al., 1994). This type of kinetics may explain the impetus to study slow-release formulations of some cephalosporins in this species (Guerrini et al., 1986). However, in spite of the rapid clearance of cephalosporins and their low to medium tissue distribution, they have been described as viable antibacterial agents for the treatment of respiratory diseases in dogs (Harpster, 1981).

Following i.m. or s.c. administration, Cp_{max} values obtained were 22 ± 3.5 μg/ml and 25 ± 3.6 μg/ml for the 20 mg/kg dose by i.m. and s.c. routes, re-

spectively, and of 15 ± 3.9 μg/ml and 16 ± 3.4 μg/ml for the 10 mg/kg dose using the same routes. These compounded activity/concentration values can be regarded as sufficient for most infections, including those caused by a great variety of Gram-negative and Gram-positive bacteria, as isolated during this study. Minimum inhibitory concentrations found in the literature fluctuate between 0.5 and 0.8 μg/ml and are not higher than an average of 2.5 μg/ml (Berezhinskaia et al., 1990; Viladrich et al., 1996; Hunfeld et al., 2000; Chamberland et al., 2001). Plasma activity/concentrations were maintained above these levels for longer than 50% of the dose-interval in this study, which can explain the clinical efficacy obtained. Bioavailability was calculated to be approximately 90% for both routes. Again, there was a slightly higher AUC value by the s.c. route. This feature is ideal to continue treatment outside the clinic and minimises lesions caused by intravenous catheters. Cefotaxime has the added advantage that even though it reaches therapeutic concentrations in the central nervous system in many species (Nau et al., 1993; Viladrich et al., 1996; Tsai et al., 2000) and possibly in the dog too, it does not have any epileptogenic activity as do some other β-lactam antibacterial drugs, such as cefazolin, penicillin G benzathine, ceftriaxone, cefoperazone, and cefamandole (De Sarro et al., 1995), also regarded as suitable antibacterial agents for the treatment of septicaemia. Summarising, these results suggest that cefotaxime is a valuable antimicrobial agent for the treatment of septicaemia in dogs, particularly at 20 mg/kg i.v., *bid* or *tid*. However, despite the favourable results obtained in this study, it is worth noting that therapeutic success not only depends on the correct selection of an antibiotic. It is important to reach an early diagnosis and identify the source of the septicaemia correctly because when septicaemia has evolved there are complicating factors, such as disseminated intravascular coagulation and multiple organ failure, requiring complex supportive therapy and in which antibacterial treatment has only secondary importance. Finally, it is important to point out that a definitive cure (including a bacteriologic cure) and not only clinical recovery, could take much longer periods of treatment than the time needed for clinical recovery in this study. This feature was not evaluated.

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