Iranian Journal of Veterinary Research, Shiraz University, Vol. 9, No. 3, Ser. No. 24, 2008

Short Paper

Pharmacokinetics of tetracycline hydrochloride after single intravenous injection in dogs

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(Received 27 Aug 2007; revised version 15 Nov 2007; accepted 2 Jan 2008)

Summary

Six mixed-breed apparently healthy dogs were intravenously administered a single dose of tetracycline hydrochloride (50 mg/kg) to evaluate the pharmacokinetic parameters of the drug. Blood samples were collected before and at various time intervals after the administration of the drug. Serum tetracycline concentrations were determined over a 24 h period using fluorescence spectrophotometry. Non-compartmental analysis of the data indicated that tetracycline has a half-life of 4.4 h, a body clearance of around 0.7 ml/kg.min and a volume of distribution of about 0.3 L/kg. The pharmacokinetics of tetracycline found in this study is favourable for therapeutic use in the dog.

Key words: Pharmacokinetics, Tetracycline, Dog

Introduction

Tetracyclines are broad-spectrum bacteriostatic antibiotics active against various bacteria, rickettsia, mycoplasma, and chlamydia (Riviere and Spoo, 2001). Tetracyclines were first introduced for clinical use in 1952 and are relatively safe that can be used as therapeutic agents as well as growth promoters in animal production (Kniffen *et al*., 1989). All tetracyclines share a 4-benzene ring structure. Functional groups attached to the basic ring structure, results in the wide variety of tetracyclines available. These compounds are amphoteric molecules with three acidic dissociation constants (Riviere and Spoo, 2001). Rational use of antimicrobial drugs to treat infectious diseases caused by bacterial agents requires knowledge not only of the bacterial susceptibility to the drug but also of the concentration of the drug that can be achieved in the animal's body fluids (Anadon *et al*., 1985). Moreover, drug dosage regimens are derived from knowledge of the pharmacodynamics and pharmacokinetics of the drug. Tetracycline pharmacokinetics and pharmacodynamics represent a relatively under-investigated but interesting area of antimicrobial chemotherapy (Agwuh and MacGowan, 2006). The factors that determine dosage of an antimicrobial agent include extent of distribution and rate of elimination of the drug, range of therapeutic (effective but non-toxic) serum concentration, accessibility to site of infection and whether the action is bacteriostatic or bactericidal at therapeutic levels (Baggot *et al*., 1977). Relatively little has been published on the pharmacokinetics of tetracycline in dogs and variety of the available data may be related to the method of analysis, route of administration, or drug formulation. The purpose of the present study was to determine the basic disposition kinetics of tetracycline in dogs after single intravenous

administration.

Materials and Methods

Animals

Six apparently healthy mixed-breed male dogs weighing 12 to 25 kg were used. The animals were kept in separate cages and had access to water and food *ad libitum*.

Drugs

Powder of tetracycline hydrochloride was pooled from the available drug dosage form (250 mg capsules, Daroopakhsh, Tehran, Iran). The amount of antibiotic solution, made by dissolving the drug in distilled water, needed for each animal was calculated on the basis of the individual body weight and a correction factor based on the purity of the drug solution compared with the standard tetracycline hydrochloride (Lot no. K21003089, Merck Co., Germany). Acepromazine maleate (1%; Alfasan, Holland; Batch No. 095306-3) was purchased from usual supplier.

Experimental design

Each dog was premedicated with the sedative drug, acepromazine (0.5 mg/kg), followed by insertion and fixation of an intravenous catheter into the right jugular vein. All animals were administered a single dose of tetracycline hydrochloride (50 mg/kg) using intravenous route via cephalic vein. Blood samples were collected from the jugular vein at various time intervals (5 min before and 5, 15, 30 and 60 min, and 1.5, 2, 3, 4, 6 and 24 h after administration of tetracycline). Sera were separated by centrifugation at 1500 g for 15 min and stored at -20°C until drug analysis, using fluorescence spectrophotometry (Chang *et al*., 1992; Rajaian and Soleimani, 2007). The recovery of tetracycline was 88.5 ± 2.7% (mean ± SEM; n = 5; C.V. <10%). The sensitivity of the test was >2 µg/ml.

Pharmacokinetic analysis

Blood concentration-time data were analysed by non-linear least squares regression analysis. A non-compartmental analysis was used to estimate major pharmacokinetic parameters from serum concentration-time data (Wilson *et al*., 1985). Area under the concentration-time curve from time zero to infinity (AUC) was obtained by the trapezoidal rule with extrapolation to infinite time by dividing the last available serum concentration value by the terminal elimination rate constant. Apparent first-order rate constants for distribution and elimination (α and β or K_{el}, respectively) were obtained from the slopes of the initial and terminal phases of the log concentration-time data, and distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively) were calculated from $0.693/K_{el}$. Drug clearance (Cl_B) and apparent volume of distribution (V_d) were calculated from Dose/AUC and Dose/(AUC × K_{el}), respectively.

Results

After intravenous injection of tetracycline hydrochloride (50 mg/kg), an initial concentration of about 0.8 mg/ml was attained in serum (Table 1). Six h post-administration, the concentration decreased to less than one fiftieth (i.e., to about 43 µg/ml). Twenty-four h after dosing, no detectable concentration of tetracycline was found in the sera. The mean log serum concentration-time plot for tetracycline was non-linear (Fig. 1); and its disappearance from the dog blood seemed to be bi-exponential with a relatively rapid

Table 1: Concentrations of tetracycline hydrochloride (Mean ± SE) in serum samples obtained at various time intervals after single intravenous injection of the drug (50 mg/kg) in dogs

Time (h)	Serum concentration (µg/ml)
0.08	764.1 ± 176.3
0.25	490.8 ± 135.0
0.5	333.5 ± 120.9
1.0	241.3 ± 53.4
1.5	208.6 ± 45.1
2.0	170.0 ± 44.3
3.0	137.3 ± 29.8
4.0	80.5 ± 69.8
6.0	42.8 ± 38.4
24.0	ND[a] (<2)

[a] Not detectable

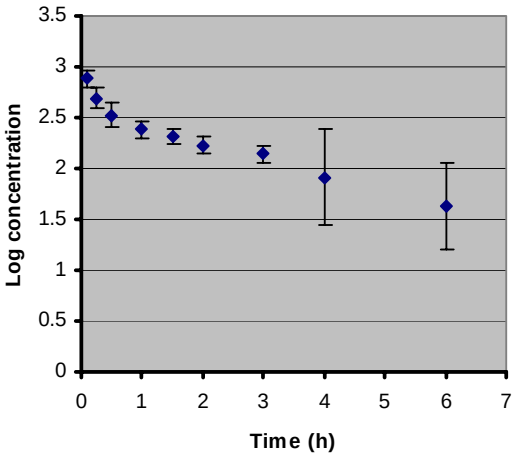

Fig. 1: Plot of log serum drug concentration versus time after single intravenous injection of tetracycline hydrochloride (50 mg/kg) in dogs

distribution phase ($t_{1/2\alpha}$<1 h) followed by a slow elimination phase ($t_{1/2\beta}$ of more than 4 h; Table 2). The apparent volume of distribution of tetracycline was about 0.3 L/kg. In addition, the blood clearance of tetracycline in dogs was calculated to be 0.7 ml/min.kg (Table 2).

Table 2: Pharmacokinetic parameters obtained for tetracycline hydrochloride after single intravenous injection of the drug (50 mg/kg) in dogs

Pharmacokinetic	
Parameters	Values
C_1 (μg/ml)	764
V_d (L/kg)	0.26
AUC (μg.h/ml)	1212
α (/h)	0.80
β (/h)	0.16
$T_{1/2\alpha}$ (h)	0.9
$T_{1/2\beta}$ (h)	4.4
Cl (ml/kg.min)	0.7

C_1, concentration of tetracycline in the first sample after intravenous administration of tetracycline (50 mg/kg); V_d, apparent volume of distribution; AUC, area under the serum concentration versus time from time zero to infinity; Cl, clearance; α, distribution phase rate constant; β, elimination phase rate constant; $t_{1/2\alpha}$, distribution phase half-life and $t_{1/2\beta}$, elimination phase half-life

Discussion

The recommended oral dosage of tetracycline to treat most susceptible bacterial infections in dogs is about 20 mg/kg every eight h (Riviere and Spoo, 2001). However, in this study no apparent adverse clinical sign was noticed in animals receiving a relatively high single dose (50 mg/kg) of tetracycline hydrochloride intravenously.

Concentration of tetracycline decreased to less than 2 μg/ml during 24 h post-administration. Taking into consideration that the antimicrobial activity of tetracycline in biological fluids will be achieved at concentrations higher than 0.5 μg/ml (Pijpers *et al*., 1990), this activity can be possibly attainable with administration of the drug with the specified dosage at 24-h intervals.

Although a non-compartmental analysis was used to estimate the pharmacokinetic parameters, but disposition behaviour for tetracycline, administered intravenously to dogs, agrees with the two-compartment open model previously described for cows and ewes (Ziv and Sulman, 1974), chickens (Anadon *et al*., 1985) and sheep (Rajaian and Soleimani, 2007). Table 3 illustrates the pharmacokinetic characteristics of various tetracycline compounds in dogs, and tetracycline in some other species. Kinetic parameters for tetracycline in dogs are similar to those found in chickens and sheep (Table 3), but relatively marked differences were found among the pharmacokinetic parameters for tetracycline in dogs versus pigs (Kniffen *et al*., 1989) and rabbits (Percy and Black, 1988).

Relatively small volume of distribution of tetracycline (0.3 L/kg) may indicate that tetracycline poorly diffuses out of blood vessels and, therefore, the drug comprises a low distribution characteristic. This may be related to the lipophobic nature of the compound (Hoeprich and Warshauer, 1974). Schach von Wittenau and Twomey (1966) reported that the distribution of tetracyclines correlates well with their lipid solubility. The volume of distribution of tetracycline after intravenous injection of the drug in dogs is around one-fourth of the value found in rabbits (Percy and Black, 1988), but is close to the values reported for chickens

Table 3: Summary of data available about pharmacokinetics of tetracyclines in various species

Drugs	Parameters						References
	Species	Dosage (mg/kg)	V_d[a] (L/kg)	K_{el}[b] (/h)	$t_{1/2}$[c] (h)	Cl_B[d] (ml/min.kg)	
Tetracycline	Man	5	-	-	7-8	-	Hoeprich and Warshauer, 1974
Tetracycline	Dogs	50	0.3	0.16	4.4	0.7	Present study
Tetracycline	Cows and ewes	20	3.3	0.12	5.7	6.6	Ziv and Sulman, 1974
Tetracycline	Man	5	1.3	-	6-11	-	Agwuh and MacGowan, 2006
Tetracycline	Chickens	65	0.2	0.25	2.8	1.6[e]	Anadon *et al*. 1985
Tetracycline	Rabbits	10	1.1	0.35	2.0	6.1	Percy and Black, 1988
Tetracycline	Pigs	11	4.5	0.04	16.0	3.1	Kniffen *et al*. 1989
Tetracycline	Sheep	20	0.2	0.21	3.3	0.7	Rajaian and Soleimani, 2007
Oxytetracycline	Dogs	5	2.0	0.12	5.7	4.2	Baggot *et al*. 1977
Minocycline	Dogs	5	2.0	0.10	6.9	3.4	Wilson *et al*. 1985
Doxycycline	Dogs	5	1.5	0.07	10.4	1.7	Wilson *et al*. 1988
Doxycycline	Dogs	5	0.9	0.1	7.0	1.7	Riond *et al*. 1990
Doxycycline	Dogs	5	0.7	0.15	4.6	1.7	Bidgood and Papich, 2003

[a] Apparent volume of distribution; [b] Elimination rate constant; [c] Elimination half-life; [d] Clearance and [e] Considering other data, this value should be about 0.8 ml/min.kg

(Anadon *et al*., 1985) and sheep (Rajaian and Soleimani, 2007). The highest apparent volume of distribution is found in pigs (Table 3). The volume of distribution of tetracycline in dogs is generally less than the values for oxytetracycline (Baggot *et al*., 1977), doxycycline (Wilson *et al*., 1988; Riond *et al*., 1990; Bidgood and Papich, 2003) and minocycline (Wilson *et al*., 1985) in this species.

The drug elimination half-life for tetracycline in dogs is not different from those reported in chickens and sheep (Table 3). In addition, the longest half-life (about 16 h) is reported for tetracycline in pigs (Kniffen *et al*., 1989) followed by doxycycline in dogs (Wilson *et al*., 1985; Riond *et al*., 1990), tetracycline in man (Hoeprich and Warshauer, 1974; Agwuh and MacGowan, 2006), tetracycline in cows and ewes (Ziv and Sulman, 1974) and sheep (Rajaian and Soleimani, 2007). The shortest half-lives belong to tetracycline in rabbits and chickens and to doxycycline in dogs (Table 3). The longest half-life of tetracycline in pigs reported by Kniffen *et al*. (1989) compared to the values found in dogs for doxycycline and minocycline may be due to the method of analysis, as in pigs the data were analysed using a three-compartments model, but a non-compartmental model was adapted to analyse the data in dogs.

Clearance of tetracycline in dogs is similar to the value found in sheep and close to that found in chickens (Anadon *et al*., 1985). Moreover, the largest clearance value is reported for tetracycline in cows and ewes (Ziv and Sulman, 1974) followed by tetracycline in rabbits (Percy and Black, 1988), oxytetracycline and minocycline in dogs (Baggot *et al*., 1977; Wilson *et al*., 1988), tetracycline in pigs (Kniffen *et al*., 1989), doxycycline in dogs and tetracycline in chickens (Anadon *et al*., 1985).

In conclusion, the discrepancies found between pharmacokinetic properties of tetracycline in dogs and in other domestic animals illustrate the importance of the pharmacokinetic studies for establishing a correct dosage regimen for an optimal therapy.

Acknowledgement

This research was financially supported by Shiraz University which is greatly appreciated.

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