Pharmacokinetics of Doxycycline in Dogs

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ABSTRACT

Six adult dogs were given doxycycline hyclate at a dosage of 5 mg/kg of body weight intravenously so that pharmacokinetic parameters could be evaluated. Serum doxycycline concentrations were determined over a 48 h period using a modified agar well bioassay. Compartmental pharmacokinetic evaluation of the serum concentration time data indicated that doxycycline has a half-life of 10.36 h, a body clearance of 1.68 ± 0.44 mL/min/kg, and a volume of distribution at steady state of 1.468 ± 0.237 L/kg. Doxycycline pharmacokinetics are favorable for therapeutic use in the dog.

RÉSUMÉ

Cette expérience portait sur six chiens et elle consistait à leur administrer de l'hyclate de doxycycline, par la voie intraveineuse, à raison de 5 mg/kg, afin de pouvoir en évaluer les paramètres pharmacocinétiques. Les auteurs déterminèrent la concentration de l'antibiotique précité, au cours d'une période de 48 heures, à l'aide d'une technique microbiologique modifiée, à base de cupules de gélose. L'évaluation par tranche de la pharmacocinétique des données relatives à la concentration sérique de l'antibiotique expérimental, en fonction du temps, révéla qu'il possédait une demi-vie de 10,36 heures, une clairance corporelle de 1,68 ± 0,44 mL/min/kg et un volume de distribution, à l'état stable, de 1,468 ± 0,237 L/kg. La doxycycline possède une pharmacocinétique favorable à son utilisation thérapeutique, chez le chien.

INTRODUCTION

Doxycycline is a broad-spectrum bacteriostatic antibiotic which is synthetically derived from oxytetracycline. Although its chemical structure is only slightly different from its parent compound considerable differences exist in its relative lipid solubility and degree of serum protein binding (1,2). Doxycycline has greater lipid solubility which accounts for superior absorption following oral administration, and for good distribution to various body tissues (1,3,4). These characteristics, and an effective antibacterial activity against anaerobic and facultative Gram-negative bacteria suggest that doxycycline may have therapeutic usefulness in the dog (5-7).

Limited studies with doxycycline in the dog report half-lives ($t_{1/2}$) of 7.3, 10 and 12 h (2,8). The variation in $t_{1/2}$ was dependent on the method of analysis (calculated or graphic), route of administration, or drug formulation. Complete pharmacokinetic data have not been reported. The purpose of the present study was to determine the pharmacokinetic values of doxycycline hyclate in the dog so that rational therapeutic regimens may be formulated.

MATERIALS AND METHODS

The experiment followed guidelines equivalent to those in "Guide to the Care and Use of Experimental Animals," Volumes 1 and 2, Canadian Council on Animal Care. Three male and three female adult (one to seven years of age) crossbred dogs (mean weight ± SD = 19.2 ± 6.3 kg) were used. During a 4 wk conditioning period the dogs were vaccinated (Canine Distemper-Hepatitis-Parainfluenza-ParvoVirus Modified Live Virus Vaccine and Leptospirosis Bacterin, Pitman-Moore, Inc., Washington Crossing, New Jersey), and were treated for internal (Task, Shell Chemical Co., Houston, Texas), and external parasites (Paramite, Vet-Kem Inc., Dallas, Taxas). They were housed indoors in temperature controlled runs (21 ± 1°C) and were fed a commercial diet (Wayne Formula One, 18% Protein, Allied Mills, Chicago, Illinois) and water *ad libitum*.

The dogs were weighed and given doxycycline hyclate (Vibramycin, Pfizer Laboratories Division, New York) at a dose of 5 mg/kg of body weight by rapid intravenous (IV) injection into the cephalic vein. It was administered as a 1% w/v solution in sterile water. Blood samples (10 mL) were obtained through previously placed jugular catheters before administration of doxycycline (0 sample) and at 0.05, 0.1, 0.15, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36 and 48 h postinjection. The blood was allowed to clot and the serum was separated by centrifugation and stored at -20°C until assayed for antibiotic content.

Doxycycline concentrations in serum were determined using a modified agar-well microbiological assay which had a minimum detection limit of 0.05 μg/mL of serum (9). *Bacillus cereus* var *mycoides* (ATCC 11778) was used as the test organism. The mean zone of inhibition of three replicates of each sample at each time period was compared with a standard curve prepared from serum with known amounts of doxycycline

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added. Total serum protein estimates were obtained by refractometer prior to doxycycline injection.

Pharmacokinetic analysis of each dog's concentration-time data was performed with a weighted, linear pharmacokinetic computer program designed for microcomputers (RSTRIP, MicroMath, Inc., Salt Lake City, Utah). The program is capable of modeling data into a maximum of five compartments, with the model of best-fit based on modified Akaike Information criterion. Values were weighted by the inverse square of the concentration. The computed pharmacokinetic values were calculated with standard equations (10). Abbreviations are those approved by the Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology (11), and are defined in Table II. Data are reported as the mean ± SD except for the $t_{½\lambda 1}$ and $t_{½}$ which are reported as the harmonic mean (12).

RESULTS

The total serum protein was 6.46 ± 0.66 g/dL, and was considered within the normal range. Rapid intravenous injection produced no observable changes in the physical condition of any of the dogs. Serum doxycycline concentrations reached apparent distribution equilibrium at 1.5 to 2 h, remained above 2 μg/mL for 8 h, and above the assay sensitivity in all six dogs for 48 h (Table I). Based upon modified Akaike Information criterion the model of best-fit was a two compartment open model. The pharmacokinetic variables are presented in Table II.

DISCUSSION

The tetracycline group of antibiotics vary widely in their pharmacokinetic values due to differences in their lipid solubility, their degree of protein binding, and their method of elimination (7). For example, while the $t_{½}$ of 10.36 h found in the present study is similar to that previously reported for doxycycline in dogs (2,8), it is somewhat longer than the 7 and 6 h reported for minocycline and oxytetracycline respectively (13,14). These differences in $t_{½}$ may be related, at least in part, to the mechanisms by which the tetracyclines are eliminated (7). The dog eliminates 90% of a single dose of doxycycline within 48 h in a nonmetabolized form (15). Sixteen percent of this dose is found in the urine (2) with the remainder eliminated by intestinal excretion (15). Doxycyline is believed to diffuse directly from the vasculature into the intestinal lumen, an effect of the drug's excellent lipid solubility. Once in the gut reabsorption is prevented by the increasing intraluminal pH of the descending gut and subsequent polyvalent cationic chelation (16). Thus, the intestinally excreted drug is inactive, but has not been metabolized by the liver. Biliary excretion accounts for less than 5% of the total elimination (2,16). On the other hand, oxytetracycline appears to be eliminated primarily by glomerular filtration, with more then 50% of the total dose found in the urine (2). Minocycline however, appears to be eliminated in both the feces and urine in a manner similar to that observed with doxycycline (17).

The (V_{ss}) for doxycycline of 1.468 L/kg is less than reported for either minocycline or oxytetracycline, and suggests the relative effect of lipid solubility and protein binding on this parameter. For instance, minocycline which is the most lipid soluble of the tetracycline group (1), is only slightly less protein bound than doxycycline (75% vs 80-85%) (2), yet has a V_{ss} of 1.9 L/kg (13). In contrast, oxytetracycline is less completely protein bound

TABLE I. Doxycycline Serum Concentrations (μg/mL) in Six Dogs After Intravenous Bolus Injection of 5 mg/kg

Postinjection Hours	Mean ± SD Serum Concentration
0.05	9.75 ± 1.78
0.1	7.33 ± 2.06
0.15	5.87 ± 1.40
0.25	5.30 ± 1.28
0.5	4.33 ± 1.14
0.75	3.65 ± 0.86
1	3.12 ± 0.64
1.5	2.87 ± 0.52
2	2.64 ± 0.52
3	2.51 ± 0.37
4	2.43 ± 0.40
5	2.29 ± 0.35
6	2.22 ± 0.37
8	2.09 ± 0.35
12	1.71 ± 0.48
24	0.66 ± 0.30
36	0.25 ± 0.15
48	0.14 ± 0.08

TABLE II. Pharmacokinetic Values Obtained From Six Dogs After Intravenous Bolus Injection of Doxycycline at 5 mg/kg

	Dog Number						
Variable (Units)	1	2	3	4	5	6	Mean ± SD
C_1 (μg/mL)	10.26	7.29	10.10	5.32	8.20	9.71	8.48 ± 1.94
C_z (μg/ml)	3.98	2.64	3.92	3.28	3.04	2.92	3.30 ± 0.55
C(O) (μg/mL)	14.22	9.93	14.02	8.59	11.24	12.63	11.77 ± 2.26
λ_1 (h^{-1})	3.20	4.36	11.80	4.23	10.02	8.17	6.96 ± 3.54
λ_z (h^{-1})	0.052	0.048	0.073	0.070	0.075	0.084	0.067 ± 0.014
$t_{½\lambda 1}$ (h)	0.22	0.16	0.06	0.16	0.07	0.08	0.09[a]
$t_{½}$ (h)	13.35	14.38	9.52	9.90	9.28	8.26	10.36[a]
MRT (h)	18.50	20.14	13.53	13.92	13.13	11.53	15.12 ± 3.39
AUC (μg h/mL)	79.81	56.39	54.72	48.06	41.57	36.02	52.76 ± 15.34
CL (mL/min/kg)	1.04	1.48	1.52	1.73	2.00	2.31	1.68 ± 0.44
V_c (L/kg)	0.352	0.504	0.357	0.582	0.445	0.396	0.439 ± 0.090
V_{ss} (L/kg)	1.158	1.783	1.236	1.446	1.581	1.601	1.468 ± 0.237
V_z (L/kg)	1.207	1.838	1.255	1.485	1.612	1.656	1.509 ± 0.243

[a]Harmonic mean

C_1 = intercept of ordinate by fastest disposition slope minus intercept of slowest disposition slope, C_z = intercept of ordinate of slowest disposition slope, C(0) = initial plasma concentration, λ_1 = fastest disposition rate constant, λ_z = slowest disposition rate constant, $t_{½\lambda 1}$ = half-life associated with the distribution rate constant, $t_{½}$ = elimination half-life associated with the terminal slope, MRT = mean residence time, AUC = area under the plasma concentration-time curve from zero to infinity, CL = total body clearance from the plasma, V_c = volume of the central compartment, V_{ss} = volume of distribution at steady state, V_z = volume of distribution during the terminal phase determined by the area method

(25-29%) (2), is markedly less lipid soluble than the other two drugs (1), yet has the greatest distribution volume (V_z of 2.1 L/kg) (14). Thus, it appears with this group of drugs that protein binding plays the dominant role in relative distribution.

Body clearance is a measure of drug elimination from the body without reference to the mechanism by which it is removed. It is therefore an important pharmacokinetic parameter, and is useful in determining the rate of drug accumulation. Values for (CL) obtained in the present study for doxycycline were 1.68 mL/min/kg, and are less then those reported for minocycline (3.3 mL/min/kg) (13) or for oxytetracycline (4.2 mL/min/kg) (14). This low clearance of doxycycline along with its long $t_{½}$ and good distribution volume suggests characteristics which are favorable for therapeutic usage in the dog.

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