Pharmacokinetics of clindamycin HCl administered intravenously, intramuscularly and subcutaneously to dogs

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A buffered aqueous solution of clindamycin Hcl (200 mg/mL) was injected intravenously (i.v.) intramuscularly (i.m.) and subcutaneously (s.c.) in a non-randomized, partial cross-over trial involving six male and six female dogs. Blood samples were collected at conventional, predetermined time periods and serum drug concentrations were determined by microbiological assay. Dogs were observed clinically for signs of pain, and activity of serum creatine phosphokinase (CPK) was monitored after i.m. dosing.

The i.v. data from five of the dogs best fitted a two-compartment open-system pharmacokinetic model whereas a non-compartment model was most suitable for analysis of the data from the remaining seven dogs. The mean i.v. elimination half-life ($t_{½\beta}$) and the mean residence time (*MRT*) were 124 and 143 min, respectively. The mean volume of distribution at steady state (V_{ss}) was 0.86 L/kg. Little pain was recorded upon i.m. injection; mean peak serum drug concentration (C_{max}) was 4.4 μg/mL, the elimination half-life ($t_{½el}$) was 247 min and the calculated bioavailability (*F*) was 115% of the i.v dose. Serum CPK activity was elevated to 25-fold the pretreatment level in samples collected 4, 8 and 12 h after i.m. injection. Pain was not recorded after s.c. drug administration; the mean C_{max} of 20.8 μg/mL was significantly greater than the corresponding value for the i.m. route, and *F* was 310%. The s.c. route appears to be superior to the i.m. route in terms of local tolerance and serum drug level; a 10 mg/kg SID treatment regimen is suggested for treatment of canine infections due to clindamycin sensitive bacteria.

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INTRODUCTION

A semisynthetic derivative of lincomycin, clindamycin has been shown to be clinically effective and is recommended for treatment of staphylococcal and anaerobic infections of skin, soft tissue and bone in dogs (Berg *et al.*, 1984; Greene, 1989; Braden *et al.*, 1988; Braden *et al.*, 1987). Clindamycin is available for parenteral administration as the 2-phosphate and hydrochloride. Clindamycin 2-phosphate is microbiologically inactive, but is hydrolized *in-vivo* to clindamycin (Webber *et al.*, 1980). The pharmacokinetics of clindamycin phosphate in dogs were studied after single intravenous (i.v.) and intramuscular (i.m.) administrations at 11 mg/kg clindamycin (Webber *et al.*, 1980) and after single subcutaneous (s.c.) injections at 2.75, 5.5, 11 and 21 mg/kg clindamycin (Webber *et al.*, 1980). Based on the pharmacokinetics of the drug, s.c. dosage regimen of 11 mg/kg of clindamycin free base as clindamycin-2-phosphate/kg body weight every 24 h was recommended (Budsberg *et al.*, 1992). The i.m. administration of clindamycin-2-phosphate solution (50 mg/mL) induced signs of pain and other side-effects and, therefore, this route was not recommended (Budsberg *et al.*, 1992). A buffered 20% aqueous solution of clindamycin hydrochloride (200 mg/mL) is available for pharmacokinetic and clinical testing. The purpose of this study was to determine the concentrations of clindamycin in normal canine serum after single i.v., i.m. and s.c. administrations of clindamycin HCl and compare the derived kinetic variables with those obtained earlier in dogs injected with equal doses of clindamycin phosphate (Webber *et al.*, 1980; Budsberg *et al.*, 1992). Local tolerance and appearance of side-effects following i.m. and s.c. administrations were particularly examined.

MATERIALS AND METHODS

Animals

Twelve adult mixed breed dogs, six males and six females (4–13 kg b.w.) were used in the study. All dogs were housed in the test facility for 3 weeks prior to the study. Dogs had free access to

water and commercial dry dog ration before and during the study. Inclusion criteria included normal findings on physical examination, complete blood count (CBC) serum concentrations of urea nitrogen, creatinine, albumin, total protein glucose, bilirubin, triglycerides, cholesterol, calcium, magnesium, sodium, potassium, chlorides,inorganic phosphorus and serum activities of alkaline phosphataes, alanine aminotransferase, aspartate aminotransferase and amylase were determined. Dogs selected for the study exhibited normal CBC and blood biochemistry test results.

Experimental design

Intravenous protocol

Jugular vein catheters were placed in each dog; patency of each catheter was maintained with heparinized saline. A blood sample was taken prior to the beginning of the trial. Each dog was given the 20% buffered aqueous clindamycin HCl i.v. at 10 mg/kg. Blood samples were obtained at 10, 20, 30, 40, 50, 60, 80, 90, 120, 180, 240, 360, 480 and 600 min post injection. Blood was allowed to clot at 20°C for 2 h and was then centrifuged at $1000 \times \boldsymbol{g}$; the serum was collected and stored at −20°C until it was assayed.

Intramuscular and subcutaneous protocols

A 2 week rest period was allowed for all dogs. All indwelling jugular venous catheter was placed and maintained as for the i.v. protocol, and a baseline blood sample was taken. The injection site (4×4 cm^2 area) on the dorsal aspect of the left and right sites were then shaved to remove short hair. Nine dogs received a single i.m. injection of the 20% clindamycin HCl at 10 mg/kg in the left-side of the neck and the remaining three dogs received a single i.m. injection of 3–5 mL sterile physiological saline in the neck. Two weeks later, nine dogs were prepared by procedures identical to those used before i.m. drug administration. Six dogs received a single s.c. injection of 20% clindamycin HCl at 10 mg/kg in the right-side of the neck. All dogs were observed immediately following i.m. and s.c. injections for evidence of pain, itching or irritation. The injection sites on both sides of the neck were palpated at each blood sampling time and at least two-times per day on the following 2 days and any abnormal finding such as pain, swelling and discoloration were recorded.

Blood samples were obtained at 15, 30, 60, 90, 150, 210, 270, 390, 510, 630, 720 and 1440. min post i.m. injection. Blood samples were collected at 30, 45, 60, 90, 120, 180, 240, 360, 480, 600, 720 and 1440 min post s.c. injection. Blood samples were processed as for after i.v. injection.

Clindamycin analysis

Clindamycin concentrations were measured by microbiological well/agar plate diffusion assay as previously described (Bennett *et al.*, 1966). The assay organism *S. lutea* ATCC 9341, was inoculated into antibiotic Medium No. 1 (Difco, Detroit, MI, USA) and a 7.0 mm layer seeded medium was added to each Petri Plates. Six wells, 8 mm in diameter, were cut into the agar at equal distances. A 50.0 µL aliquot of samples (and standard clincamycin HCl solution) was alternately added to each well and the plates were incubated at 37°C for 14–16 h. The concentration of drug in each sample was calculated from zone of inhibition diameters using polinomial regression techniques. Sensitivity limit of assay method was 0.1 µg/mL. Standard curves were derived using clindamycin HCl (Sigma Chemical Co. St. Louis, MO, USA) in dog serum. The correlation coefficient of the standard curve from 0.10 to 6.0 µg/mL was 0.99 ($P < 0.001$). Samples with concentrations > 6.0 µg/mL were diluted with antibiotic-free dog serum to bring clindamycin concentrations within the range of the standard curve. The coefficients of variation of repeatedly assayed samples at concentrations ranging between 1 6 µg/mL and 0.1 1.0 µg/mL were 7.5% and 12.5%, respectively. Samples were assayed in duplicate and data are reported as mean ± SD. It was recognized that this assay fails to distinguish between clindamycin and its putative active metabolites and, therefore, results were expressed as serum clindamycin antimicrobial equivalent activity. Thus the term 'clindamycin concentration' where used throughout this report is rather clindamycin antimicrobial equivalent activity.

Serum creatine phosphokinase (CPK)

Serum CPK values were determined, using as enzymatic method (CK-NAC-active creatine kinase EC2.7.3.2, Randox Laboratories Ltd., Crumlin, Northern Ireland), in blood samples collected at 0, 4, 8, 12, 24, 32, 48 and 72 h after nine dogs were injected i.m. with 20% clindamycin HCl solution, three dogs were injected with saline, three dogs were injected s.c. with 20% clindamycin HCl and three dogs were administered saline s.c. As large differences in pretreatment CPK values were found among the dogs examined, serum CPK data were converted to percentage by dividing each post treatment value by the pretreatment value for the corresponding animal. The post treatment CPK data are presented as mean ± SD-fold rise from pretreatment (baseline) CPK value.

Data analysis

Estimates of first-order rate constants and volumes were initially obtained by subjecting mean data to analysis, using iterative least squares regression analysis (Brown & Manno, 1978). The concentrations vs. time data from each dog were then analysed, using a microcomputer program for nonlinear weighted least square regression (Bourne, 1986).

The most appropriate pharmacokinetic model was selected on the basis of the lowest weighted sum of squares and the lowest Akaike's information criterion (AIC) value (Yamaoka *et al.*, 1978) for data from each dog. The i.v., i.m. and s.c. areas under the curves (AUCs) were calculated using trapezoidal approximations between time of drug administration and 1440 min afterwards. Differential calculus methods (Edwards & Penney, 1982) were used to estimate peak serum drug concentrations (C_{max}) and time of C_{max} (t_{max}) after i.m. and s.c. administrations. Kinetic values are presented as mean ± SD; half lives, however, are presented as harmonic mean ± pseudo-SD (Lam *et al*, 1985). The paired Student's *t*-test was used for calculating the significance of the differences in the mean kinetic values for the i.m. and s.c. routes; $P < 0.05$ value was considered significant.

RESULTS

Clinical signs indicative of slight pain were noticed in four to five of the dogs immediately following i.m. injection; the remaining dogs did not exhibit any pain reaction. Signs suggesting pain or discomfort were not shown by any dog after s.c. injection. Palpation of the injection site did not elicit any pain reaction. Local changes could not be felt at the injection site. Thus, the neck side injected with clindamycin HCl could not be differentiated from the side injection with sterile saline solution.

Mean serum clindamycin concentrations after i.v., i.m. and s.c. administrations are presented (Table 1). Data are also presented graphically as mean log10 serum concentrations vs. time plot (Fig. 1). The i.v. data from five of the dogs best fitted a two-compartment open system pharmacokinetic whereas a one-compartment model was most suitable for analysis of data from the remaining seven dogs. Thus, the kinetic values Cp°, A, and $t_{½\alpha}$ presented (Table 2) represent data from these five dogs; it shows a rapid rate of drug distribution from the central to the peripheral body compartment. The elimination half-life ($t_{½\beta}$) and the mean residence time (*MRT*) were 124.0 ± 57.0 min and 143.0 ± 34.0 min, respectively and the steady state volume of distribution (V_{ss}) was 0.86 ± 0.35 l/kg. After i.m. drug administration, the mean C_{max} (4.4 ± 0.5 μg/mL) was significantly ($P < 0.05$) lower than the corresponding value for the s.c. administration (20.8 ± 6.2 μg/mL).

The mean absorption time (*MAT*) of clindamycin HCl solution injected s.c. was significantly shorter than after i.m. administration. The mean $t_{½el}$ i.m. value (427.0 ± 209.0 min) was not significantly different from the mean $t_{½el}$ for the s.c. route (310.2 ± 190.4 min) but these values were significantly longer than the mean i.v. $t_{½\beta}$. The mean s.c. *AUC* was significantly larger than the mean i.m. *AUC* and the resulting calculated bioavailability *(F)* values which were 1.15 and 3.1 for the i.m. and s.c. routes, respectively (Table 3).

Serum CPK activity rose sharply within 8 h after i.m/ injection of clindamycin HCl; activity returned to pretreatment level by 48 h post treatment. A minimal rise in serum CPK activity was observed after s.c. clindamycin injection. The i.m. and s.c. administration of saline did not affect serum CPK activity.

DISCUSSION

The clinical manifestations of pain described (Budsberg *et al.*, 1992) following i.m. administration of 5% solution of clindamycin phosphate to dogs were not seen at all after i.m. injection of more concentrated (20%) buffered aqueous solution of clindamycin HCl. We can only speculate on the causes for these differences in local tolerance; they could be due to the type of clindamycin salt, the presence of buffer or a four-fold smaller volume injected using the 20% clindamycin HCl solution. The transient rise in serum CPK activity observed after i.m. injection of clindamycin HCl to dogs (Fig. 2) indicates some degree of muscle tissue damage at the injection site (Steinnes *et al.*, 1978). However, a similar or even higher and more persistent rise has been documented for a long list of apprived veterinary injectable products which are very commonly used in small and large animal practice without any observable pain reactions (Rasmussen, 1980; Svendsen, 1983). A better safety evaluation of i.m. clindamycin HCl therapy must wait until data from multiple injections are available. The present

Table 1. Mean serum clindamycin concentrations (μg/mL) after intravenous, intramuscular and subcutaneous injection of clindamycin HCl to dogs at 10 mg/kg body weight

	Treatment					
	Intravenous $n=12$		Intramuscular $n=9$		Subcutaneous $n=6$	
Time (min)	Mean	SD	Mean	SD	Mean	SD
10	13.4	2.3	NS		NS	
15	NS		2.6	0.76	NS	
20	11.3	2.2	NS		NS	
30	10.2	2.3	3.6	0.90	16.8	12.8
40	8.9	2.5	NS		NS	
45	NS		NS		19.5	3.8
50	7.7	1.8	NS		NS	
60	6.8	1.4	4.0	0.60	17.4	6.7
80	5.75	0.6	NS		NS	
90	5.6	1.3	4.0	0.70	13.5	4.1
120	4.1	0.87	NS		12.6	4.6
150	NS		3.5	0.50	NS	
180	3.0	0.7	NS		10.7	3.2
210	NS		3.0	0.40	NS	
240	2.1	0.45	NS		6.9	2.2
270	NS		2.3	0.40	NS	
360	0.82	0.22	NS		4.6	1.4
390	NS		1.7	0.40	NS	
480	0.46	0.10	NS		3.3	1.8
510	NS		1.1	0.40	NS	
600	0.31	0.11	NS		2.7	1.6
630	NS		0.70	0.30	NS	
720	NS		0.60	0.30	1.7	1.2
1440	NS		0.30	0.10	0.3	0.1

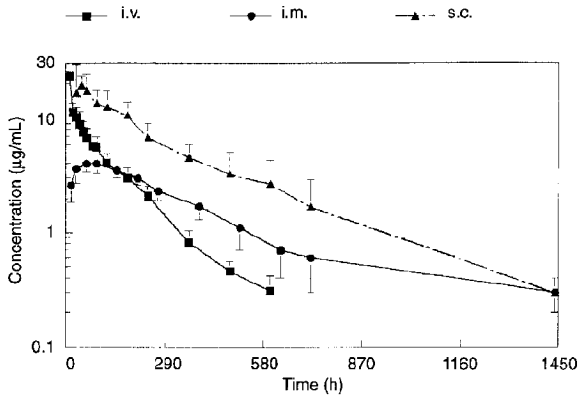

Fig. 1. Serum clindamycin concentrations (μg/mL, log 10 scale) after intravenous, intramuscular and subcutaneous administration of clindamycin HCl to dogs at 10 mg/kg.

Table 2. Selected pharmacokinetic values for clindamycin HCl administered intravenously to 12 dogs at 10 mg/kg

Kenetic value & unit	Mean	SD
Cp°, μg/mL	18.75	3.71
A, μg/mL	11.06	3.35
B, μg/mL	7.54	3.35
$t_{½\alpha}$, min	11.00	13.30
$t_{½\beta}$, min	124.00	57.00
MRT, min	143.00	34.00
V_c, L/kg	0.56	0.11
V_{ss}, L/kg	0.86	0.35
AUC, μg/mL.min	1457.00	280.00
Cl_t, mL/min/kg	6.10	1.10
r^2	0.967	0.031

A = ordinal intercept of fastest disposition slope minus the intercept of the slowest disposition slope; B = ordinal intercept of the slowest disposition slope; Cp° = initial serum concentration; $t_{½\alpha}$ = distribution half-life; $t_{½\beta}$, elimination half-life; *MRT* = mean residence time; V_c = volume of the central compartment; V_{ss} = volume of distribution at steady state; *AUC* = area under the concentration-time cutve from zero to 24 h post-treatment; Cl_t = total body clearance; r^2 = correlation coefficient to the line of best fit for a two-compartment open system pharmacokinetic.

Table 3. Selected pharmacokinetic values for clindamycin administered intramuscularly and subcutaneously to dogs at 10 mg/kg

	Treatment			
Kinetic value and unit	Intramuscular $n = 9$		Subcutaneous $n = 6$	
	Mean	SD	Mean	SD
C_{max}, μg/mL	4.4	0.5	20.8	6.2
t_{max}, min	73.0	16.0	46.7	20.1
MAT, min	546.0	226.0	224.5	163.5
$t_{½el}$, min	427.0	209.0	310.2	190.4
MRT, min	700.0	246.0	364.2	147.3
AUC, μg/mL min	1806.0	346.0	5258.0	2161.0
F(*)	1.15	0.19	3.10	0.22

C_{max}, peak maximal serum concentration; t_{max}, time to peak serum concentration; *MAT* = mean absorption time, calculated as $MRT_{non\text{-}i.v.} - MRT_{i.v.}$; *F** = bioavailability, calculated as $AUC_{non\text{-}i.v.}/AUC_{i.v.}$

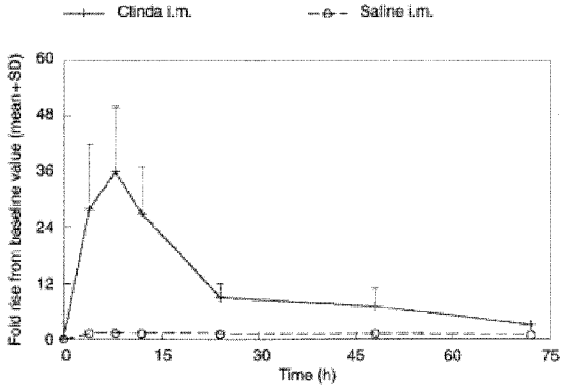

Fig. 2. Serum CPK activity in dogs after intramuscular administration of clindamycin HCl at 10 mg/kg.

findings clearly indicate that the s.c. route is superior to the i.m. route in terms of local tolerance.

Interpretation of data gathered in the course of the present study must take into consideration the assay method used (microbiological). Although a good agreement was shown between microbiological and chemical (GC) test results in dog serum for clindamycin (Ziv & Shem-Tov, unpublished data), there is a slight chance that there are some putative active metabolites. The disposition curves after i.v. administration of clindamycin HCl was best represented as a two-compartment open model in only five of the dogs. The i.v study protocol we used called for collecting the first post treatment blood sample at 10 min.

Because of the rapid distribution rate of the drug in the dog ($t_{½\alpha}$ of 3.5 ± 1.1 min) according to (Budsberg *et al.*, 1992), we probably missed observing the distribution phase. Values for the other major kinetic parameters found in the present study were also different from the values calculated in dogs injected i.v. with clindamycin phosphate (Budsberg *et al.*, 1992). Thus, mean $t_{½\beta}$, *MRT* and *AUC* after clindamycin phosphate administration were 194.6 min, 263.4 min and 2009.5 μg·mL, respectively. Such differences in kinetic values, although small, could result from the rate of appearance of bioactive antibiotic in the serum after i.v. administration of the microbiologically inactive clindamycin phosphate, differences in body-weight (clindamycin phosphate was injected to dogs weighting 20 to 30 kg), (Budsberg *et al.*, 1992) or slightly different methods used for calculating the kinetic variable. On the other hand, mean Cl_t, V_c, and V_{ss} for clindamycin phosphate were very close to the corresponding values for clindamycin HCl estimated in the present study. Regardless of these small differences, the large V_{ss} of clindamycin indicates possible wide distribution in the body fluids and tissues. Direct measurements of tissue clindamycin concentrations in humans (Panzer *et al.*, 1972; Dhawan & Thadepalli, 1982) and cats (Brown *et al.*, 1990) confirmed these assumptions.

The kinetic variables calculates from the i.m. serum drug level data for clindamycin HCl and clindamycin phosphate were in good agreement. The short t_{max} (1h) and average bioavailability of nearly 100% support rapid and complete absorption of the drug from the site of i.m. injection, as was remarked earlier (Budsberg *et al.*, 1992). The kinetic profile of the drug in serum of all dogs after s.c administration of clindamycin HCl is rather unique; mean C_{max} (20.8 μg/mL) was nearly 4.5 times greater than the mean i.m. C_{max}. Moreover, mean serum concentrations during the first 12 h post treatment by the s.c. route were two to three-fold higher than the concentrations found after i.m. drug administration (Fig. 1). After a nearly equivalent dose of the drug (11 mg/kg) was injected s.c. to dogs as clindamycin phosphate (Webber *et al.*, 1980) a mean C_{max} of 6.1 ± 0.3 μg/mL was recorded at t_{max} of 40–60 min. We found that the terminal elimination rate of the drug from serum ($t_{½el}$) after s.c. administration of 20% clindamycin HCl solution (310.2 ± 190.4 min) was considerably longer than the reported (Budsberg *et al.*, 1992) $t_{½el}$ of 234.8 ± 27.3 min after an equivalent dose was given to dogs i.m. as clindamycin phosphate. A $t_{½el}$ of 13.9 h was calculated (Webber *et al.*, 1980) from the serum clindamycin data of dogs injected s.c. with clindamycin phosphate.

It appears therefore, that s.c. administration of clindamycin HCl allows for rapid, complete drug absorption and, at the same time, acts as a depot which limits the rate of drug elimination from serum. A entero-hepatic circulation effect was suggested to operate in dogs treated orally with clindamycin HCl (Lavy *et al.*, 1999) contributing to the prolongation of $t_{½el}$ to nearly 6 h, and for calculated oral bioavailability values exceeding 100%. Whatever the pharmacokinetic processes involved, it appears from the present study that the s.c. route is superior to the i.m. in practical terms by permitting a longer treatment interval.

Earlier studies (Braden *et al.*, 1987; Budsberg *et al.*, 1992) attempted to establish i.v. and i.m. dosing recommendations using average serum concentrations at steady state with the accompanying peak (Cp_{max}) and through (Cp_{max}) concentrations as means for calculating (Gibaldi, 1982; Riviere, 1988) dosage regimens for clindamycin phosphate in dogs. The calculated dosage schedule was eventually found to be in agreement with the currently recommended oral dosage schedule of 11 mg/kg, q 12 h (Budsberg *et al.*, 1992). We have tried to use a similar approach for selecting desirable, potentially antibacterial effective, serum drug concentrations in dogs given clindamycin HCl by s.c. route. In relating the minimal inhibitory concentration (*MIC*) of clindamycin to its pharmacokinetic properties it has been assumed (Webber *et al.*, 1980; Budsberg *et al.*, 1992; Brown *et al.*, 1990; Riviere, 1988) that: (a) tissue drug concentration at least equal to the MIC is maintained throughout the entire dose interval; (b) the drug is minimally bound to serum protein and serum concentrations are equal to, or even slightly lower than, the concentration in major target sites of the body (excluding bone); (c) the kinetic profiles of the drug in serum and the target tissue on multiple dosing are very similar; and (d) the *MIC* for *Staphylococcus aureus/intermedius* ranges from 0.04 to 0.4 μg/mL and for most anaerobic bacteria, the *MIC* ranges from 0.1 to 3.1 μg/mL but the *MIC* 90 is in effect > 1.6 μg/mL (Greene, 1989; Budsberg *et al.*, 1992; Brown *et al.*, 1990). Using the mean serum concentration values, we observed that a single s.c. 10 mg/kg SID dosage regimen appears to be appropriate for clindamycin HCl for the treatment of staphylococcal soft tissue infections. For anaerobic infections, however, this treatment should be given BID. A more intensive course of clindamycin therapy is apparently required for the treatment of staphylococcal bone infections in the dog (Braden *et al.*, 1987; Braden *et al.*, 1988; Budsberg *et al.*, 1991).

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