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DISPOSITION KINETICS AND DOSAGE OF CEPHALORIDINE IN CALVES

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SUMMARY

The disposition kinetics and dosage regimen of cephaloridine were investigated in calves following a single intravenous dose of 10 $mg \cdot kg^{-1}$. The distribution half-life and elimination half-life were $0 \cdot 16 \pm 0 \cdot 02$ and $1 \cdot 96 \pm 0 \cdot 16$ h, respectively. The apparent volume of distribution was $0 \cdot 64 \pm 0 \cdot 06$ $l \cdot kg^{-1}$ and total body clearance which represents the sum of all clearance processes, was $225 \cdot 2 \pm 15 \cdot 1$ $ml \cdot kg^{-1} \cdot h^{-1}$. Based on kinetic parameters, a satisfactory intravenous dosage regimen of cephaloridine in calves would be $11 \cdot 0$ $mg \cdot kg^{-1}$ repeated every 8 h.

INTRODUCTION

Cephaloridine, a semisynthetic antibiotic, is effective against a wide range of microorganisms (Tally *et al.*, 1981; Sanders & Sanders, 1983). Among other factors, the therapeutic efficacy of an antibiotic is dependent on a suitable dosage regimen, so that during the course of therapy the concentration of drug in blood and target organs should not fall below the minimum effective concentration. The disposition kinetics of cephaloridine have been studied in man and laboratory animals (Gold, McKee & Ziv, 1973; Kirby & Regamey, 1973) but only limited information is available in domestic animals (Ziv, Shani & Sulman, 1973). The purpose of the present study was to determine the disposition kinetics and dosage regimen of cephaloridine in calves after single intravenous administration.

MATERIALS AND METHODS

Five healthy male cross-bred calves weighing 104–134 kg were kept in the departmental animal shed with free access to food and water and maintained under uniform conditions of management. Cephaloridine (Ranbaxy Lab. Ltd, India) was injected into the jugular vein of animals at the dose rate of 10 $mg \cdot kg^{-1}$ as a 5% solution in normal saline.

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Blood samples were withdrawn from the contralateral jugular vein at various predetermined time intervals up to 8 h after administration of drug. Plasma was collected and kept at −20°C until analysis, usually on the next day.

The concentration of cephaloridine in plasma was estimated by employing the microbiological assay technique using *Sarcina lutea* (ATCC 9341) as test organism (Simon & Jongyin, 1970; Arret, Johnson & Krishbaum, 1971). This method permits the detection of 0·5 $\mu g \cdot ml^{-1}$ of cephaloridine. Kinetic parameters were determined according to the method of computed least squares. The rate constant of distribution phase was obtained by the method of residuals (Gibaldi & Perrier, 1975). Based on these data a suitable dosage regimen was calculated (Baggot, 1977).

RESULTS AND DISCUSSION

The plasma concentrations of cephaloridine as a function of time were plotted on a semilogarithmic scale (Fig. 1). The distribution and elimination phases are also shown. Evaluation of the results revealed that the disposition of cephaloridine was adequately described by a bi-exponential equation, $Cp = Ae^{-\alpha t} + Be^{-\beta t}$, where Cp is cephaloridine concentration at time t, A and B are zero-time intercepts of initial and terminal phases of

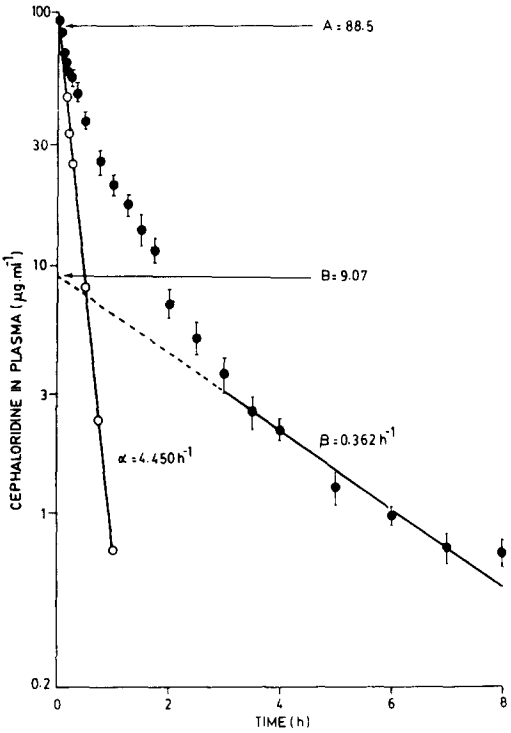

Fig. 1. Semilogarithmic plot of plasma concentration–time profile of cephaloridine in calves following a single intravenous dose (10 $mg \cdot kg^{-1}$). Values are given as mean ± SE of five animals. Distribution (α) and elimination (β) phases are represented by least square regression lines. The calculated points (O) of distribution phase were obtained by feathering technique.

plasma concentration-time curves, α and β are the distribution and elimination rate constants, respectively and e represents the base of natural logarithm. The pharmacokinetics of cephaloridine have also been reported to follow a two-compartment open model in cows and ewes (Ziv *et al.*, 1973).

At 1 min the plasma level of cephaloridine was $93{\cdot}4 \pm 3{\cdot}05\ \mu g \cdot ml^{-1}$ which was approximately 90-fold higher than the minimum therapeutic plasma level.

The levels of cephaloridine in central and peripheral compartments of a representative animal were derived from the pharmacokinetic model and plotted on a semilogarithmic scale (Fig. 2). The pattern of drug movement from central to peripheral compartment reflects the apparent equilibrium between blood and tissues which was achieved within 40 min of administration. When apparent equilibrium was attained, the ratio of drug level in peripheral to central compartment was always more than 2. This was maintained up to 8 h.

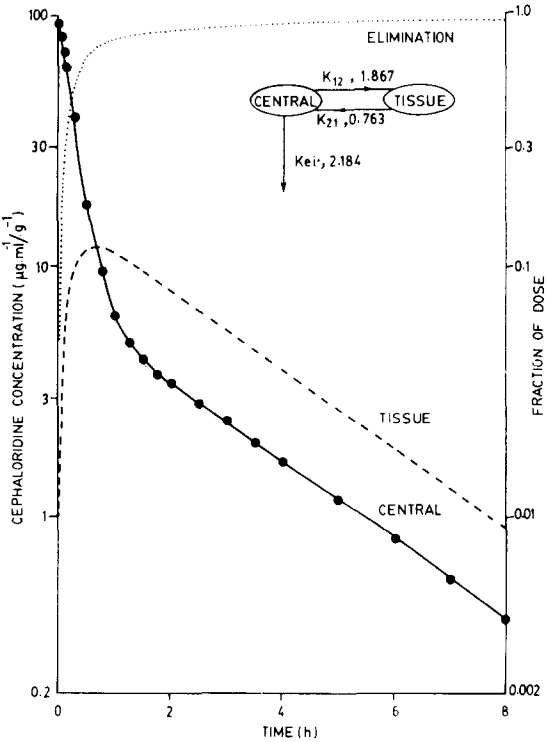

Fig. 2. Cephaloridine levels (fraction of dose) in central and peripheral compartments and fraction of dose eliminated as a function of time in a representative animal. A scheme of two-compartment open model showing values of its first order rate constants is shown in inset.

Table I represents the calculated values of disposition kinetic parameters of cephaloridine in calves. The high value of rate constant α ($4{\cdot}45 \pm 0{\cdot}36\ h^{-1}$) indicated that cephaloridine is rapidly distributed in body fluids and tissues which was further substantiated by high value of K_{12}/K_{21} ($2{\cdot}47 \pm 0{\cdot}17$). The calculated apparent volume of distribution ($0{\cdot}64 \pm 0{\cdot}06\ l \cdot kg^{-1}$) reflected good penetration of cephaloridine in body fluids and tissues. The total body clearance and T/P ratio of cephaloridine was

Table I
Kinetic parameters of cephaloridine in calves after single intravenous dose of 10 mg/kg body weight

Parameter[a]	*Unit*	*Mean* ± *SE*[b]
Cp_o	$\mu g \cdot ml^{-1}$	97·7 ± 2·76
A	$\mu g \cdot ml^{-1}$	88·5 ± 3·07
α	h^{-1}	4·45 ± 0·36
$t_{1/2\alpha}$	h	0·16 ± 0·02
B	$\mu g \cdot ml^{-1}$	9·07 ± 1·78
β	h^{-1}	0·36 ± 0·03
$t_{1/2\beta}$	h	1·96 ± 0·16
K_{12}	h^{-1}	1·87 ± 0·30
K_{21}	h^{-1}	0·76 ± 0·12
K_{12}/K_{21}	Ratio	2·47 ± 0·17
K_{el}	h^{-1}	2·18 ± 0·09
$t_1/2K_{el}$	h	0·32 ± 0·01
AUC	$\mu g \cdot ml^{-1} \times h$	45·2 ± 3·07
$V_{d(area)}$	$l \cdot kg^{-1}$	0·64 ± 0·06
$V_{d(B)}$	$l \cdot kg^{-1}$	1·27 ± 0·22
$V_{d(ss)}$	$l \cdot kg^{-1}$	0·36 ± 0·03
Cl_B	$ml \cdot kg^{-1} \cdot h^{-1}$	225·2 ± 15·1
td	h	6·52 ± 0·54
T/P	Ratio	5·19 ± 0·59

[a]Kinetic parameters have been described by Gibaldi & Perrier (1975).
[b]Values are from five animals.

calculated to be 225·2 ± 15·1 $ml \cdot kg^{-1}\ h^{-1}$ and 5·19 ± 0·59, respectively. The elimination half-life of cephaloridine in calves was 1·96 ± 0·16 h. A shorter elimination half-life of cephaloridine (0·6 ± 0·1 h) has been reported in cows and ewes compared with calves (Ziv *et al.*, 1973). The elimination half-life value of cephaloridine has been reported as 1·4 h in man (Brogard *et al.*, 1976).

A satisfactory dosage regimen of cephaloridine in calves may be computed by employing the kinetic parameters established in the present investigation. The antimicrobial activity of antibiotics depends on their plasma concentration during the course of therapy which should not fall below certain concentration [$Cp\,(\min)^{\alpha}$]. For cephaloridine a concentration of 0·004–1·0 $\mu g \cdot ml^{-1}$ is considered an effective concentration (Weinstein, 1975); in this calculation 1 $\mu g \cdot ml^{-1}$ was used.

When a fixed dose of drug is repeated at constant time intervals, a steady state will eventually be established at which the plasma concentration–time curve will be the same during the subsequent dose intervals. The minimum steady state concentration ($Ab^{-\alpha}$) at the end of each dosing interval is calculated by the following formula (Wagner & Northam, 1967)

$$Ab^{-\alpha} = D/[V_{d(area)}(e^{\beta\tau} - 1)]$$

where D=dose, $V_{d(area)}$=apparent volume of distribution, e=base of natural logarithm, β=elimination rate constant, τ=dose interval. On this basis, the minimum steady state concentration of cephaloridine in plasma 8 h after the administration of 10 $mg \cdot kg^{-1}$ dose will be 0·91 $\mu g \cdot ml^{-1}$ which is close to the desired effective concentration (1 $\mu g \cdot ml^{-1}$).

After obtaining a suitable dose interval, the maintenance dose (D') of cephaloridine can be calculated by the formula

$$D' = Cp(\min)^{\alpha} \cdot V_{d(area)}(e^{\beta\tau} - 1).$$

The priming dose (D) is obtained by omitting -1 from the above equation. Taking 8 h as a suitable dosage interval, with a minimum therapeutic plasma level (Cp $(\min)^{\alpha}$) of 1 $\mu g \cdot ml^{-1}$ and using the values of β and $V_{d(area)}$ of Table I, the priming and maintenance doses of cephaloridine were determined in calves at a dose rate of 11·6 $mg \cdot kg^{-1}$, repeated at 8 h intervals at 10·9 $mg \cdot kg^{-1}$ body weight; in practice it would be 11 $mg \cdot kg^{-1}$ repeated at 8 h intervals.

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