Veterinary Research Communications, 17 (1993) 313–323

PHARMACOKINETICS OF BENZYDAMINE IN DAIRY COWS FOLLOWING INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION

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ABSTRACT

Anfossi, P., Malvisi, J., Catraro, N., Bolognini, M., Tomasi, L. and Stracciari, G.L., 1993. Pharmacokinetics of benzydamine in dairy cows following intravenous or intramuscular administration. *Veterinary Research Communications*, **17 (4)**, 313–323

Five lactating cows were given benzydamine hydrochloride by rapid intravenous (0.45 mg/kg) and by intramuscular (0.45 and 1.2 mg/kg) injection in a crossover design. The bioavailability, pharmacokinetic parameters and excretion in milk of benzydamine were evaluated. After intravenous administration, the disposition kinetics of benzydamine was best described using a two-compartment open model. Drug disposition and elimination were fast ($t_{½\alpha}$: 11.13 ± 3.76 min; $t_{½\beta}$: 71.98 ± 24.75 min; MRT 70.69 ± 11.97 min). Benzydamine was widely distributed in the body fluids and tissues ($V_{d(area)}$: 3.549 ± 1.301 L/kg) and characterized by a high value for body clearance (33.00 ± 5.54 ml/kg per min). After intramuscular administration the serum concentration–time curves fitted a one-compartment open model. Following a dose of 0.45 mg/kg, the C_{max} value was 38.13 ± 4.2 ng/ml at a t_{max} of 67.13 ± 4.00 min; MAT and MRT were 207.33 ± 22.64 min and 278.01 ± 12.22 min, respectively. Benzydamine bioavailability was very high (92.07% ± 7.08%). An increased intramuscular dose (1.2 mg/kg) resulted in longer serum persistence (MRT 420.34 ± 86.39 min) of the drug, which was also detectable in milk samples collected from both the first and second milking after treatment.

Keywords: benzydamine, bioavailability, cattle, milk, pharmacokinetics

Abbreviations: HPLC, high-pressure liquid chromatography; IC_{50}, concentration to inhibit the activity of an organism by 50%; IM, intramuscular(ly); IV, intravenous(ly); NSAID, non-steroidal antiinflammatory drugs; pK_a, negative logarithm of the ionization constant (K_a) of a drug; other abbreviations are listed in footnotes to tables

INTRODUCTION

Benzydamine (*N*,*N*-dimethyl-3-[[1-(phenylmethyl)-1H-indazol-3-yl]oxy]-1-propanamine; Figure 1) is a non-steroidal anti-inflammatory drug whose activity is mainly directed toward primary normoreactive types of inflammation. There is evidence that

this drug differs from other NSAIDs in its mode of action. The available data show that benzydamine exerts no inhibitory effects on the arachidonic acid cascade or on amino acid decarboxylases, and that it does not affect the sulphydryl-group reactivity.

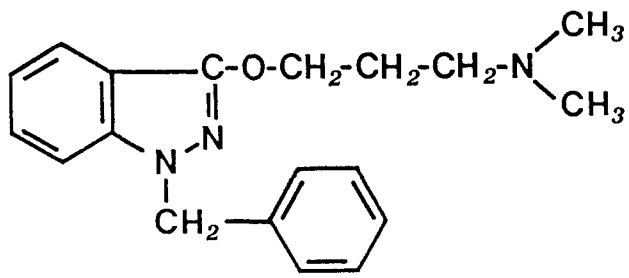

Figure 1. Structure of benzydamine

Benzydamine inhibits platelet aggregation independently from cyclooxygenase inhibition and exerts a stabilizing effect on the erythrocyte membrane unrelated to protein stabilization. Furthermore, it inhibits capillary vasodilatation and reduces the overproduction of mucopolysaccharides that occurs in inflammatory processes (Cioli *et al.*, 1985; Segre and Hammarström, 1985; Silvestrini *et al.*, 1966a,b; White, 1988).

Benzydamine is indicated for topical or systemic application in humans and animals in order to obtain relief of inflammatory syndromes in the oropharynx, respiratory tract and in the genitourinary and gastrointestinal systems. No data are currently available on the pharmacokinetics of benzydamine in animals, despite its use in veterinary medicine.

The objectives of the present study were to determine the bioavailability of benzydamine, its pharmacokinetic parameters and its excretion in milk by cows given single IV or IM injections of the drug at different dose levels.

MATERIALS AND METHODS

Animals

Five healthy Rendena dairy cows were used. These were aged between 3 and 6 years, weighed from 450 kg to 650 kg, were held in fixed stalls and were producing 15–20 litres of milk per day.

Drug administration

Benzydamine hydrochloride as a 3% injectable aqueous solution (Tantum Iniettabile 3%, ACRAF SpA, Rome, Italy) was administered to the animals according to a three-way crossover design. The intervals between treatments were 15 days.

The IV injections of the drug were given via the jugular vein at 0.45 mg/kg body weight, while the IM injections were made into the neck muscles at either 0.45 mg/kg body weight or 1.2 mg/kg body weight.

Blood sampling

Blood samples (8 ml) were collected from the jugular vein just prior to dosing and at 10, 20, 30, 40 and 50 min and 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after administration. After IM dosing with 1.2 mg/kg, the blood samplings were carried out at the same time, and also at 36, 48, and 72 h.

Serum was obtained by centrifugation for 15 min at 2000*g* and kept at −20°C until the assay.

Milk sampling

Milk samples (250 ml) were collected from cows treated IM with 1.2 mg/kg of benzydamine hydrochloride before dosing and then at 6 milkings after treatment. The time intervals between the treatment and the milkings were approximately 9, 23, 33, 47, 57 and 71 h. The samples were stored at −20°C.

Benzydamine assay

Extraction. Serum: 1.5 ml of acetonitrile was added to 0.5 ml of serum, vortex-mixed for 15 s and centrifuged for 15 min at 2000*g*. Supernatant (1 ml) was dried (UniEquip, Laborgerätebau & Vertrieb AN, Kraupa, Martinsried, Germany) and the residue was dissolved in 0.25 ml of the mobile phase.

Milk: 3 ml of acetonitrile was added to 1 ml of milk, vortex-mixed for 15 s and centrifuged for 15 min at 2000*g*. Supernatant (2 ml) was dried and the residue was dissolved in 0.5 ml of 1 mol/L NaOH. Benzydamine was extracted three times with 3 ml of heptane, by vortexing for 60 s. The heptane phase was dried and the residue was dissolved in 0.5 ml of the mobile phase.

HPLC analysis. The HPLC equipment used consisted of a Beckman 116 pump (Beckman Instruments Inc., San Ramon, CA, USA) and a Promis II autosampler (Spark Holland BV, Emmen, The Netherlands) coupled to a Jasco 812FP fluorescence detector (Japan Spectroscopic Co., Tokyo, Japan) operated at an excitation wavelength of 303 nm and an emission wavelength of 355 nm. Chromatograms and peak area values were recorded using the software System Gold release 4.0 (Beckman Instruments Inc., San Ramon, CA, USA). The column used was a Nova Pack C18 (150 × 3.9 mm ID, 5 μm particle size; Waters, Milford, MA, USA). The mobile phase was acetonitrile–water–acetic acid (62:37.5:0.5, v/v) and contained 20 mmol/L sodium dodecyl sulphate. The mobile phase flow rate was 1.5 ml/min. An injection volume of 10 μl was used at all times.

Standard solutions of benzydamine were prepared in methanol using benzydamine hydrochloride powder (purity grade, 99.9%, ACRAF). Calibration curves were obtained from samples of control (drug-free) serum and milk mixed with appropriate amounts of benzydamine to give concentrations of 5, 25, 50, 100, 200 and 300 ng of base/ml and analysed by HPLC as above.

The recovery by the extraction procedure from serum and milk was found to be respectively 98% and 96.5%. The limit of detection was about 2.5 ng/ml in serum and 5 ng/ml in milk.

Pharmacokinetic analysis

The experimental data obtained after intravenous administration were fitted to a two-compartment open model expressed by

$$C_s(t) = A \exp(-\alpha t) + B \exp(-\beta t)$$

where $C_s(t)$ is the serum concentration at time t, A and B are the Y-axis intercepts, and α and β are the hybrid rate constants of the distribution and elimination phases, respectively.

After intramuscular administration, since the distribution phase of benzydamine was masked by the absorption phase, the serum concentrations of drug were fitted to a one-compartment open model described by:

$$C_s(t)_{im} = -F \exp(-k_{abs} t) + G \exp(-k_{el} t)$$

where $C_s(t)_{im}$ is the serum concentration at time t after intramuscular administration, F and G are the extrapolated zero-time exponential terms, and k_{abs} and k_{el} are the absorption rate constant and the elimination rate constant, respectively.

Individual serum concentration–time data were fitted by a least-squares method using a non-linear regression program based on Marquandt's algorithm on an IBM PS2/50 personal computer (IBM United Kingdom, Portsmouth, England). The experimental data were weighted using $1/y^2$. Initial estimates of the parameters were obtained by the residual method (Gibaldi and Perrier, 1975). The following microconstants were also calculated: k_{21} $(A\beta+B\alpha/A+B)$, k_{10} $(\alpha\beta/k_{21})$ and k_{12} $(\alpha+\beta-k_{21}-k_{el})$.

The extrapolated zero-time drug concentration (C^0) after IV administration was calculated as the sum of the Y-axis intercepts, and the volume of central compartment (V_c) was calculated as the ratio Dose/C^0.

The serum concentration–time data were also analysed using statistical moments (Riegelman and Collier, 1980). The system moment mean residence time (MRT) was determined using the equation MRT = AUMC/AUC, where AUC is the area under the concentration–time curve from time 0 to infinity and AUMC is the area under the moment curve extrapolated to infinite time. AUC and AUMC were calculated using the linear trapezoidal method and extrapolation to infinite time was made as follows:

$$AUC_{t^*-\infty} = C^*/\lambda$$

$$AUMC_{t^*-\infty} = t^*C/\lambda + C^*/\lambda^2$$

where t^* is the last time with measurable concentrations (C^*) and λ is the elimination rate constant (β or k_{el}).

The mean absorption time (MAT = MRT_{im}–MRT_{iv}), the steady-state volume of distribution ($V_{d(ss)}$ = Dose × AUMC/AUC^2), the volume of distribution by area ($V_{d(area)}$ = Dose/AUC×β) and the body clearance (Cl_B = Dose/AUC) were also calculated.

The half-lives were calculated from the rate constants obtained by compartmental analysis ($t_{½}$ = 0.693/rate constant) and also from MRT ($t_{½el}$ = 0.693×MRT) and from MAT ($t_{½abs}$ = 0.693×MAT).

The bioavailability after intramuscular administration (F) was determined according to:

$$F = \frac{AUC_{im}}{AUC_{iv}}$$

RESULTS

Table I shows the mean ± SD serum concentration values of benzydamine obtained after IV administration of 0.45 mg/kg and after IM dosing with 0.45 mg/kg and 1.2 mg/kg. The semilogarithmic plots of the benzydamine serum concentration–time curves after IV and IM administration to a representative cow are shown in Figure 2.

The pharmacokinetic disposition of benzydamine in the five cows was well described by a two-compartment open model after IV administration and by a one-compartment open model after IM administration, as shown by the good correlations obtained (r^2 always >0.97).

The pharmacokinetic parameters obtained from animals treated IV are presented in Table II as means ± SD. After IV administration, the benzydamine concentration was maximal at the first sampling time (10 min) and then decreased rapidly, but the mean drug levels were still above the detection limit in serum samples collected 5 h after treatment.

The mean values of the pharmacokinetic parameters of benzydamine determined after IM administration are listed in Table III. The essential bioavailability following a dose of 0.45 mg/kg was very high, the mean value being >90%. When the benzydamine was given IM at 1.2 mg/kg it could still be detected in the serum after 1440 min. After IM administration at 1.2 mg/kg, benzydamine could only be detected in milk samples from the first and second milkings after treatment, at mean concentrations of 25.82 ± 3.37 ng/ml and 8.50 ± 0.63 ng/ml, respectively.

TABLE I
Mean (± SD) serum concentrations of benzydamine after intravenous and intramuscular administration to five dairy cows

Time (min)	Serum concentrations (ng/ml)		
	0.45 mg/kg IV	0.45 mg/kg IM	1.2 mg/kg IM
10	231.48 ± 44.79	17.64 ± 4.76	46.76 ± 15.20
20	159.16 ± 30.05	24.40 ± 3.24	65.42 ± 23.94
30	110.72 ± 18.08	30.96 ± 5.31	77.26 ± 26.50
40	84.18 ± 10.22	36.42 ± 6.33	82.60 ± 29.22
50	72.14 ± 10.65	39.84 ± 6.44	86.14 ± 29.58
60	52.68 ± 9.63	39.74 ± 4.90	84.62 ± 28.19
120	27.20 ± 8.00	33.78 ± 1.93	74.26 ± 22.02
180	14.06 ± 5.41	27.80 ± 3.40	60.32 ± 12.95
240	8.34 ± 2.44	20.96 ± 1.69	52.18 ± 13.26
300	4.40 ± 0.82	16.28 ± 1.89	42.24 ± 9.39
360	ND[a]	13.08 ± 1.57	35.74 ± 8.29
480	ND	8.28 ± 1.59	26.64 ± 5.13
600	ND	5.42 ± 0.76	22.16 ± 4.20
720	ND	3.28 ± 0.37	13.62 ± 2.36
1440	ND	ND	3.48 ± 0.93

[a]ND = not detected

DISCUSSION

The pharmacokinetic pattern of benzydamine hydrochloride administered IV to cows is characterized by more rapid distribution and elimination phases than those described elsewhere for humans and laboratory animals. A clear difference is observable between the half-lives of benzydamine in cows (1.2 h) and in humans (7.7 h after an 8 min IV infusion of 5 mg of drug; Chasseaud and Catanese, 1985). Moreover, our results differ from those obtained by Catanese *et al.* (1966) in mice and rats that were given a far higher dose of benzydamine (10 mg/kg). Ten minutes after injection, these authors found 10 μg/ml in mice and 3 μg/ml in rats, which decreased to 3 μg/ml and 1.5 μg/ml after 2 h and to 1 μg/ml and 0.5 μg/ml after 4 h, respectively. Considering the proportional decrease in each case, a faster decrement was observed in cows, but it is difficult to compare our results with those obtained by these authors since they used a very different dosage and a relatively non-specific analytical method to determine the concentrations of the drug.

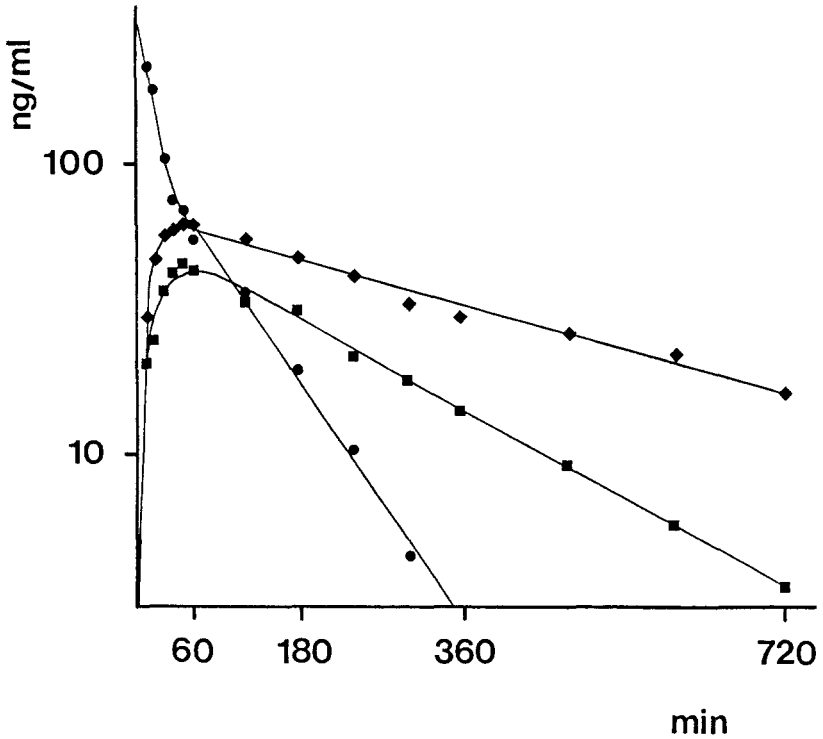

Figure 2. Semilogarithmic plots of benzydamine serum concentrations after IV (0.45 mg/kg, •) and IM (0.45 mg/kg, ▪; 1.2 mg/kg, ♦) administration of benzydamine hydrochloride in a representative dairy cow

Based on its apparent volumes of distribution ($V_{d(area)}$ and $V_{d(ss)}$), benzydamine appears to be widely distributed in body fluids and tissues. This is in good agreement with the chemical properties of this drug, characterized by a pK_a of 9.35 and a chloroform : 0.1 mol/L HCl partition coefficient of 7.8 (D. Galli Angeli, personal communication, 1992), which accounts for the large volume of distribution in humans (111 ± 22 L) following an 8 min IV infusion of 5 mg of the drug (Chasseaud and Catanese, 1985).

Giacalone and Valzelli (1966) reported higher benzydamine concentrations in tissues than in the blood of rats treated intraperitoneally with 10 mg/kg, i.e. 11.73 μg/g in the liver, 11.40 μg/g in the spleen, 8.94 μg/g in the kidney, 6.40 μg/g in the brain and 0.76 μg/ml in the blood 15 min after administration.

The high volumes of distribution for benzydamine observed in cows suggest intracellular passage and/or tissue constituent binding. However, passive diffusion into ruminal fluid and consequent ion-trapping, already described for other lipid-soluble bases (Baggot, 1977), cannot be excluded.

TABLE II
Pharmacokinetic parameters of benzydamine hydrochloride after intravenous administration (0.45 mg/kg) to five dairy cows

Parameter[a]	Units	Mean ± SD	Range
C^0	ng/ml	385.69 ± 104.20	(264.6 – 527.1)
A	ng/ml	288.98 ± 78.14	(193.7 – 375.1)
α	min^{-1}	0.0677 ± 0.0203	(0.0489 – 0.0864)
B	ng/ml	96.72 ± 44.15	(36.8 – 152.0)
β	min^{-1}	0.0105 ± 0.0032	(0.0063 – 0.0142)
k_{10}	min^{-1}	0.0285 ± 0.0045	(0.0214 – 0.0322)
k_{12}	min^{-1}	0.0242 ± 0.0098	(0.0214 – 0.0322)
k_{21}	min^{-1}	0.0255 ± 0.0105	(0.0101 – 0.0351)
$t_{½\alpha}$	min	11.13 ± 3.76	(8.02 – 16.14)
$t_{½\beta}$	min	71.98 ± 24.75	(48.83 – 109.99)
V_c	L/kg	1.193 ± 0.330	(0.824 – 1.668)
AUC	ng min^{-1} ml^{-1}	13 944 ± 2316	(11 064 – 16 379)
AUMC	ng min^{-1} ml^{-2}	979 547 ± 181 792	(665 028 – 1106 789)
MRT	min	70.69 ± 11.97	(57.88 – 84.65)
$t_{½el}$	min	48.99 ± 8.29	(40.11 – 58.66)
$V_{d(area)}$	L/kg	3.549 ± 1.301	(2.144 – 5.410)
$V_{d(ss)}$	L/kg	2.341 ± 0.573	(1.535 – 3.025)
Cl_B	ml/kg per min	33.00 ± 5.54	(26.51 – 40.68)

[a] C^0 = extrapolated zero-time drug concentration; A and B = y-axis intercepts; α and β = hybrid rate constants of the distribution and elimination phases; k_{10} = first order rate constant for drug elimination from the central compartment; k_{12}, k_{21} = first-order rate constant for drug distribution between central (1) and peripheral (2) compartments; $t_{½\alpha}$ and $t_{½\beta}$ = distribution and elimination half-lives; V_c = volume of the central compartment; AUC = area under the serum concentration–time curve; AUMC = area under the moment curve; MRT = mean residence time; $t_{½el}$ = elimination half-life obtained from analysis by statistical moment theory; $V_{d(area)}$ = volume of distribution by area; $V_{d(ss)}$ = steady-state volume of distribution; Cl_B = body clearance

The body clearance value for benzydamine (33 ml/kg per min) exceeds the renal clearances of inulin (1.4 ml/kg per min), creatinine (1.68 ml/kg per min) and diodrast (9.11 ml/kg per min) reported for cows (Baggot, 1977), as might be expected for a drug that is cleared more by hepatic than by renal elimination. Actually, the metabolism of the drug, not included in our study, probably plays the most important role in its elimination. Previous studies (Kataoka *et al.*, 1973) have shown that only 1–1.4% of an oral dose of benzydamine is eliminated in the urine of mice, rats, guinea

pigs, cats, dogs and rabbits as the parent compound, while 16.6–38.9% of the dose is excreted in urine as related compounds. This explanation could also explain the mimimal elimination of the parent drug in milk.

TABLE III
Pharmacokinetic parameters of benzydamine hydrochloride after intramuscular administration (0.45 and 1.2 mg/kg) to five dairy cows

Parameters[a]	Units	Treatment				
		0.45 mg/kg		1.2 mg/kg		
C_{max}	ng/ml	38.13	± 4.2	79.48	± 25.66	
t_{max}	min	67.13	± 4.00	47.22	± 8.15	
k_{abs}	min^{-1}	0.0362	± 0.0023	0.0817	± 0.0302	
k_{el}	min^{-1}	0.0040	± 0.0002	0.0024	± 0.0004	
$t_{½abs}$	min	19.23	± 1.23	9.39	± 3.16	
$t_{½el}$	min	175.66	± 8.76	296.91	± 52.03	
AUC	ng min^{-1} ml^{-1}	12 725	± 1347	37870	± 6694	
AUMC	ng min^{-1} ml^{-2}	3 538 893	± 425 514	16 125 416	± 2479 441	
MRT	min	278.01	± 12.22	420.34	± 86.39	
MAT	min	207.33	± 22.64			
$t_{½abs'}$	min	143.68	± 15.69			
F	%	92.07	± 7.08			

[a] C_{max} = calculated maximal concentration; t_{max} = calculated time for C_{max}; k_{abs} and k_{el} = absorption and elimination rate constants; $t_{½abs}$ and $t_{½el}$ = absorption and elimination half-lives; AUC = area under the serum concentration–time curve; AUMC = area under the moment curve; MRT = mean residence time; MAT = mean absorption time; $t_{½abs'}$ = absorption half-life obtained from analysis by statistical moment theory; F = bioavailability (× 100)

The differences between the results obtained in cows and the data reported in other species, in particular the faster disappearance of the drug from the serum in cows than in humans, could be attributed to different metabolic rates and in part to the wider distribution into the peripheral compartment in cows.

Benzydamine is well absorbed after intramuscular injection, as shown by its presence in the bloodstream 10 min after administration, its peak serum values at 50 min, and its bioavailability of 92%.

Although the formulation used was not intended for delayed absorption, the drug was probably still being absorbed from the injection site even after it had reached the peak serum concentration at 50 min. This lengthened the elimination half-life from 72

min (IV) to 176 min (0.45 mg/kg IM) and 297 min (1.2 mg/kg IM). This observation is well supported by the MAT value of 207 min and by the absorption half-life of 193 min calculated from non-compartmental analysis after IM administration at 0.45 mg/kg.

A tentative explanation of this 'delayed absorption', which seems to be dose-related, could involve the physico-chemical properties of the drug, particularly its high degree of ionization in muscle tissue, and the pH of the formulation (about 5).

The high bioavailability of benzydamine after IM administration and its more extended residence time in the body may be advantageous for therapeutic purposes. Moreover, the efficacy of this drug in inflammation could be particularly related to high tissue concentrations. As in the case of diclofenac (Willis *et al.*, 1979) and as shown by our preliminary unpublished results in rabbits, an extensive uptake and retention of the drug by tissues may explain its prolonged therapeutic effect despite its rapid disappearance from the circulation.

The tissue concentrations of benzydamine are probably of the same order of magnitude as those reported as the IC_{50} in various *in vitro* inflammation models (10^{-4}–10^{-6} mol/L; White, 1988). However, to calculate a dosage regimen we can only refer to the serum concentrations found in humans, which are higher than 200 ng/ml at about 8 h after oral administration of 50 mg (Baldock *et al.*, 1991). According to the general equation $C = V_{d(area)}\,\tau/(FD \times 1.44t_{½\beta})$, where C is the assumed efficacious concentration in humans (200 ng/ml), D is the 1.2 mg/kg dose, F is the bioavailability set at 92.07%, and $V_{d(area)}$ and $t_{½\beta}$ were set at 3.5 L/kg and 297 min, respectively, we calculate a dose interval (τ) of 11 h. Consequently, two daily administrations of benzydamine will assure therapeutic levels. However, as indicated by clinical observations in cattle (Quadri *et al.*, 1971), lower dosages might be sufficient because of the high tissue distribution of this drug.

ACKNOWLEDGEMENT

This work was supported in part by a MURST grant (MURST 40% 1990).

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(Accepted: 2 July 1993)