Bulgarian Journal of Veterinary Medicine (2001), **4**, No 2, 77 - 86.

PHARMACOKINETICS OF AMIKACIN AND AMPICILLIN IN DOGS FOLLOWING SINGLE ADMINISTRATION AND CO-ADMINISTRATION WITH FLUNIXIN MEGLUMINE IN DOGS

A. HARITOVA, D. PASHOV AND D. BAKALOV
Faculty of Veterinary Medicine, Trakia University, Stara Zagora

Summary

Haritova, A., D. Pashov and D. Bakalov, 2001. Pharmacokinetics of amikacin and ampicillin in dogs following single administration and co-administration with flunixin meglumine in dogs. *Bulg. J. Vet. Med*., **4**, No 2, 77 – 86.

The pharmacokinetics of amikacin (AMK) and ampicillin (AMP) administered intravenously independently and after intravenous administration of flunixin meglumine (FM) in 3 female and 3 male dogs has been studied.

After a single intravenous (*iv*) injection of AMP, the elimination half-life ($t_{1/2\beta}$), area volume of distribution (Vd_{area}) and total body clearance (Cl_B) were 1.41±0.09 h, 1.97±0.71 l/kg and 29.05±14.73 ml/kg.min, respectively. Under the influence of FM the values of Vd_{area} and Cl_B were 2.18±1.14 l/kg and 23.46±13.54 ml/kg.min, respectively.

After a single oral (*po*) administration of AMP the $t_{1/2\beta}$ value, mean absorption time (MAT) and absolute bioavailability (F_{abs}) were 1.02±0.17 h, 1.23±0.34 h and 24.90±8.05 %, respectively. When AMP was co-administered with FM, there was tendency towards higher antibiotic plasma levels. The MAT value, $t_{1/2\beta}$ and F_{abs} were 1.16±0.57 h, 0.916±0.13 h and 77.65±57.5 %, respectively.

After a single *iv* administration of AMK, $t_{1/2\beta}$, Vd_{area} and Cl_B were 2.28±0.11 h, 0.61±0.15 l/kg and 3.13±0.61 ml/kg.min, respectively. Under the influence of FM the respective values were 2.26±0.4 h, 0.65±0.25 l/kg and 2.78±0.58 ml/kg.min.

The co-administration of FM (*iv*) and AMP (*iv* or *po*) or AMK (*iv*) does not bring to significant changes in antibiotics pharmacokinetics.

Key words: amikacin, ampicillin, dogs, drug interactions, flunixin meglumine, pharmacokinetics

INTRODUCTION

Ampicillin (AMP) and amikacin (AMK) are antibacterial drugs, widely used in veterinary medicine, including the canine species (Baggot et al., 1985; Cabana et al., 1969; Keefe & Smith, 1977; Lavy et al., 1995; Ling & Gilmore, 1977). Very often, those antibiotics are used together with nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of bacterial infections (Hekman et al., 1982; Zarfin et al., 1985; Firth et al., 1990). At the same time, their co-administration is accompanied by pharmacokinetic interactions requiring modification of the dosage schedules of chemotherapeutics (Zarfin et al., 1985; Firth et al., 1990). During the last decade, flunixin meglumine (FM) is established as an effective analgetic, more appropriate than meperidine hydrochloride, pentasozine lactate, phenylbutazone and codeine phosphate (Hardie et al., 1985). Furthermore, it has an anti-inflammatory

activity and aids to overcome states characterized by endotoxic shock in dogs (Dunkle *et al*., 1985). Those properties of FM determine its frequent co-administration with antibiotics in dogs (Dunkle *et al*., 1985; Vonderhaar & Salisbury, 1993).

Bibliographic data about AMP pharmacokinetics in dogs after independent application are incomplete. Data for the possible pharmacokinetic interactions between FM and AMP or AMK are not available.

Our studies aimed to follow out the pharmacokinetics of AMP following single administration as well as to obtain data, justifying its co-administration with flunixine meglumine in dogs.

MATERIALS AND METHODS

Experimental animals

Six crossbred 3 female and 3 male dogs, 1-3 years old and ranging in body weight from 11.5 to 16 kg were used. They were shown to be clinically healthy by means of daily observation for 20 days, physical examination, total red cell count and total and differential white cell count. Animal care and handling were in accordance with the provisions of the European Community, as adopted by the Bulgarian Government.

Drugs

The following drugs were used: ampicillin sodium (Ampicillin, Balkanpharma Ltd, Razgrad), prepared *ex tempore* as 12.5 % aqueous solution for *iv* injection and as 6.25 % aqueous solution for oral administration); amikacin sulfate (Amikacin, 5 % injectable solution, Sopharma); flunixin meglumine (Finadyne, 5 % injectable solution, Shering Plough)[1].

Experimental design

Trials with AMP. The intravenous (*iv*) and oral (*po*) doses of AMP were 10 mg/kg and 20 mg/kg, respectively. The dogs were used in four consecutive experiments. Each experiment was followed by a 10 days washout period.

- *Experiment I.* The dogs were treated *iv* with a single dose of AMP.
- *Experiment II.* The dogs received a single *iv* dose of 1.0 mg/kg FM and a single *iv* dose of AMP in the opposite vein.
- *Experiment III.* The dogs were treated *po* with AMP.
- *Experiment IV.* The dogs received a single *iv* dose of 1.0 mg/kg FM and a single *po* dose of AMP, after a 18 h fasting.

Trials with AMK. The dogs were used in two experiments and AMK was administered *iv* at a single dose of 5 mg/kg. The treatments with AMK were initiated 30 days after the last treatment with AMP. The first experiment was followed by a 30 day washout period.

- *Experiment I.* The dogs were treated *iv* with a single dose of AMK.
- *Experiment II.* The dogs received a single *iv* dose of 1.0 mg/kg FM and a single *iv* dose of AMK in the opposite vein.

AMP or AMK were injected *iv* into the cephalic vein. Blood samples were collected from the opposite cephalic vein, using an intravenous catheter (Helm pharmaceuticals GmbH, Hamburg, Germany) 22G. They were collected before each treatment with the antibiotics and at 0.083, 0.25, 0.5, 1, 2, 4, 5, 6 and 7 h after

[1] Finadyne 5 % injectable solution was kindly supplied by the firm Shering

the administration of AMP and at 0.083, 0.25, 0.5, 1, 2, 4, 5, 6, 8 and 10 h after the administration of AMK. After oral administration of AMP blood samples were collected from the cephalic vein before each treatment with AMP and at 0.5, 0.75, 1, 2, 2.5, 3, 4, 5, 6 and 7 h thereafter.

Drug analysis

Plasma concentrations of AMP and AMK were determined by using as test microorganisms *Bacillus subtillis ATCC 6633* and *Bacillus mycoides* HB_2, respectively (Bennet et al, 1966). The limits of quantition were 0.035 μg AMP/ml and 0.18 μg AMK/ml plasma. The standard solutions were prepared in plasma obtained from untreated dogs.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated after the methods described by Baggot (1977) using a computer program. Pharmacokinetic analysis was performed using two-compartment open model for the data obtained after *iv* administration of AMK. The most appropriate model was chosen according to Akaike's information criterion (Yamaoka *et al*., 1978). Non compartmental analysis based on statistical moments theory (Gibaldi and Perrier, 1982) was also performed for the data obtained after *iv* injection of AMK and for the data obtained after *iv* and oral treatment with AMP. Because of unrealistic data for plasma AMP levels in one of the dogs, this particular case was not included in the calculations. The relevant pharmacokinetic indices determined are shown in Table 1 and Table 2. The AUC was calculated by the method of trapezoids and extrapolation to infinity was made. After oral administration, MAT values were obtained as the differences between the MRT after oral administration and the MRT after *iv* administration. The values of absolute bioavailability of AMP - F_{abs} (Prescott & Baggot, 1993) and relative bioavailability of AMP vs the combination AMP+FM - F_r (Rowland & Tozer, 1995) were also found.

The *iv* maintenance dose was determined from the equation (Baggot, 1977):

$$D = Cp_{min}.Vd_{area}.(\exp^{\beta\cdot\tau} - 1)$$

where Cp_{min} = minimum therapeutic plasma level (Cp_{min} = MIC according to Prescott and Baggot, 1993); Vd_{area} = volume of distribution based on area under the curve to infinity; β =terminal (elimination) rate constant and τ = dosage interval.

The oral maintenance dose was determined from the equation:

$$Bapp = P_{min}.(1-\exp^{-\beta\cdot\tau}) / \exp^{-\beta\cdot\tau},$$

where: Bapp = the value of the coefficient based on the terminal exponential phase used for correcting the applied dose according to the desired MIC and dosage interval (Mercer et al., 1977); P_{min}=MIC; exp=base of natural logarithm and τ =dosage interval.

The doses and dose intervals were defined with respect to the desirable values of the MIC for AMP or AMK, based upon their pharmacokinetic parameters. The doses were fixed according to the maximum allowed plasma concentrations of AMP and AMK.

Statistical analysis

Pharmacokinetic parameters were presented as mean ± SEM values. The statistically significant differences between pharmacokinetic parameters following the single administration of AMP or AMK and after co-administration with FM were determined using the Wilcoxon's tests by means of a statistical software (Statistica, Microsoft Corp., StatSoft Inc., USA, 1993). P values < 0.05 were considered significant.

RESULTS

Following the independently AMP administration, its plasma levels were higher than MIC (0.1 μg/ml) for 7 h (Fig. 1). Its biological half-life was 1.41±0.09 h, Vd_{area} - 1.97±0.71 l/kg and Cl_B - 29.05±14.73 ml/min.kg (Table 1). Following *po* application, appearance of plasma AMP concentrations was detected between hours 0.5 and 0.7, being higher than MIC between hours 2 and 4 (Fig. 2). There were significant variances in blood AMP levels among the individual dogs. The biological half-life was 1.02±0.17 h and MAT was 1.23±0.34 h. C_{max} (0.648±0.19 μg/ml) was reached for t_{max} 2.3±0.25 h (Table 1).

Table 1. Pharmacokinetic parameters of ampicillin sodium administered *iv* to 6 dogs or *po* to 5 dogs at a dose rate of 5 mg/kg, solely and with flunixin meglumine (*iv* 1 mg/kg), mean±SEM

Parameters	Ampicillin sodium	Ampicillin sodium and flunixin meglumine
Noncompartmental analysis, iv		
β (h^{-1})	0.50 ±0.03	0.547 ±0.04
$t_{1/2\beta}$ (h)	1.41 ±0.09	1.31 ±0.1
MRT (h)	1.71 ±0.21	1.68 ±0.21
Vd_{area} (l/kg)	1.97 ±0.71	2.18 ±1.14
V_{ss} (l/kg)	1.89 ±0.71	1.51 ±0.71
Cl_B (ml/min.kg)	29.05 ±14.73	23.46 ±13.54
AUC (μg.h/ml)	7.38 ±2.6	9.33 ±3.51
AUMC (μg.h^2/ml)	13.76 ±5.07	15.24 ±5.98
Noncompartmental analysis, po		
β (h^{-1})	0.76 ±0.12	0.82 ±0.11
$t_{1/2\beta}$ (h)	1.02 ±0.17	0.916 ±0.13
t_{max} (h)	2.30 ±0.25	2.50 ±0.22
C_{max} (μg/ml)	0.648 ±0.19	1.94 ±0.99
Co (μg/ml)	5.476 ±1.83	10.17 ±8.62
MRT (h)	3.19 ±0.12	2.99 ±0.29
MAT (h)	1.23 ±0.34	1.16 ±0.57
AUC (μg.h/ml)	1.25 ±0.22	3.50 ±1.67
AUMC (μg.h^2/ml)	3.968 ±0.65	9.42 ±4.22
F_{abs} (%)	24.90 ±8.05	77.65 ±57.5
F_r (%)	-	163.37 ±82.8

β - hybrid rate constant for the elimination phase; $t_{1/2\beta}$ - elimination phase half-life time; MRT - mean residence time; Vd_{area} - volume of distribution based on area under the curve to infinity; Vss - volume of distribution at steady-state; Cl_B - total body clearance; AUC - area under the concentration vs. time curve projected to infinity; AUMC - area under the first moment curve; C_{max} - peak drug concentration; t_{max} - time of C_{max} ; Co - extrapolated zero-time plasma concentration of the elimination phase; MAT - mean absorption time; F_{abs}% - absolute bioavailability; F_r% - relative bioavailability.

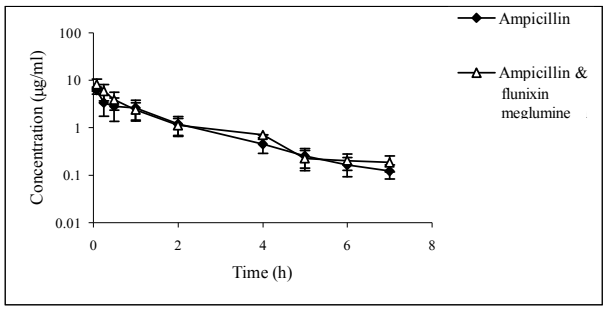

Fig. 1. Mean ± SEM plasma concentrations of ampicillin in dogs (n=6) after *iv* administration of ampicillin sodium at a dose rate of 10 mg/kg - independently and after co-administration with flunixin meglumine (*iv*) at 1 mg/kg.

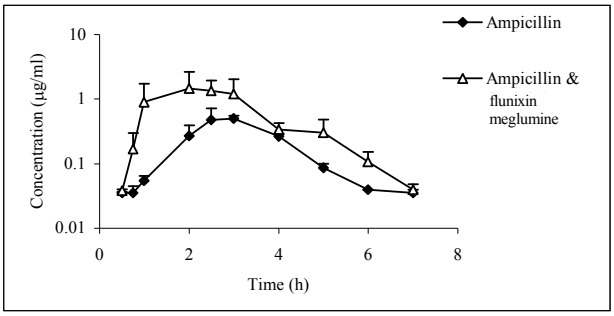

Fig. 2. Mean ± SEM plasma concentrations of ampicillin in dogs (n=5) after *po* administration of ampicillin sodium at a dose rate of 20 mg/kg - independently and after co-administration with flunixin meglumine (*iv*) at 1 mg/kg.

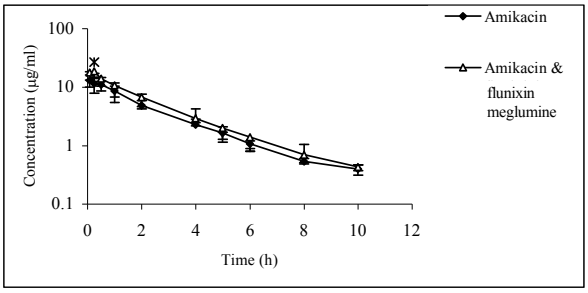

Fig. 3. Mean ± SEM plasma concentrations of amikacin in dogs (n=6) after *iv* administration of amikacin sulfate at a dose rate of 5 mg/kg - independently and after co- administration with flunixin meglumine (*iv*) at 1 mg/kg.

The *iv* AMP and FM co-administration of resulted in slightly higher plasma antibiotic levels (Fig. 1). The pharmacokinetic parameters of AMP used in the combination were not significantly changed compared to its independent *iv* injection (Table 1). Following *po* administration, at the background of FM, the

plasma antibiotic concentrations, C_{max}, t_{max} and F_{abs} showed a tendency towards increase; F_r was over 100% (Table 1, Fig. 2).

The independently *iv* administration of AMK in dogs resulted in plasma concentrations over MIC (1μg/ml) until about the posttreatment hour 5. The plasma concentration curves (Cp) plotted vs time (t) (Fig. 3) corresponded to a two-compartmental model of distribution and elimination, described by the equation:

Cp = 5.59.exp(-11.05.t) + 9.35.exp(-0.3.t).

The biological half-life was 2.28±0.3 h. The values of Vd_{area} and V_{ss} were 0.61±0.15 l/kg and 0.63±0.15 l/kg respectively (Table 2).

Following the co-administration of AMK and FM, plasma AMK levels showed a tendency towards elevation compared to the independent application of the antibiotic (Fig. 3) and remained higher than MIC (1 μg/ml) for 5 h after

Table 2. Pharmacokinetic parameters of amikacin sulfate in plasma administered *iv* to dogs (n=6) at a dose rate of 5 mg/kg, solely and with flunixin meglumine (*iv* 1 mg/kg), mean±SEM

Parameters	Amikacin sulfate	Amikacin sulfate and flunixin meglumine
Two compartmental analysis, iv		
$t_{1/2\alpha}$ (h)	0.154 ±0.11	0.157 ±0.07
$t_{1/2\beta}$ (h)	2.28 ±0.30	2.26 ±0.4
k_{12} (h^{-1})	2.43 ±1.19	1.25 ±0.65
k_{21} (h^{-1})	8.44 ±2.03	8.47 ±2.41
k_{el} (h^{-1})	0.48 ±0.07	0.54 ±0.09
V_c (l/kg)	0.428 ±0.1	0.364 ±0.11
V_t (l/kg)	0.24 ±0.09	0.184 ±0.10
Vd_{area} (l/kg)	0.61 ±0.15	0.65 ±0.25
V_{ss} (l/kg)	0.63 ±0.15	0.52 ±0.16
Cl_B (ml/min.kg)	3.08 ±0.55	2.87 ±0.59
AUC (μg.h/ml)	30.93 ±4.55	35.57 ±6.69
Noncompartmental analysis, iv		
Vd_{area} (l/kg)	0.528 ±0.096	0.519 ±0.15
V_{ss} (l/kg)	0.521 ±0.12	0.455 ±0.13
MRT (h)	2.72 ±0.21	2.595 ±0.23
AUC (μg.h/ml)	31.36 ±5.1	36.54 ±6.59
Cl_B (ml/min.kg)	3.13 ±0.61	2.78 ±0.58

$t_{1/2\alpha}$ - distribution phase half-life time; $t_{1/2\beta}$ - elimination phase half-life time; k_{el} - overall rate constant for drug elimination; k_{12} - the distribution rate constants for transferring the drug from the central to the peripheral compartment; k_{21} - the distribution rate constants for transferring the drug from the peripheral to the central compartment; Vd_{area} - volume of distribution based on area under the curve to infinity; V_c - volume of distribution of the central compartment; V_t - volume of distribution of the peripheral compartment; V_{ss} - volume of distribution at steady-state; MRT - mean residence time, AUC - area under the concentration vs. time curve projected to infinity; Cl_B - total body clearance.

the treatment. The plasma AMK concentrations (Cp) decreased with time according to the equation:

$$Cp = 5.04.\exp(-9.9.t) + 12.82.\exp(-0.352.t).$$

The parameters characterizing the disposition (Vc, Vt and Vss) and Cl_B tended to decrease (Table 2).

DISCUSSION

During the experiments, no adverse side effects were observed in experimental animals.

The biological half-life of AMP in our experiments was similar to that, reported by Lavy et al. (1995) - 1.85 h and by Cabana et al. (1969) - 1.55 h. The observed Vd_{area} was relatively high and close to the value obtained by Lavy et al. (1995) - 1.8 l/kg. It is lower than Vd_{area}, determined by Papich (1988) - 0.3-0.4 l/kg. Following *po* administration of AMP in our study, C_{max} was reached 30 min later than in the experiments of Watson et al. (1986) - t_{max}=1.6-2 h. Our F_{abs} value of 24.9 % should be compared to bibliographic data, characterized by an excessive variance. According to Baggot (1984), the bioavailability of AMP following oral administration in dogs was under 10% while Cabana et al. (1969) reported values of 57.4 %. This is most probably due to the differences in the drug formulation. Our data, being in an intermediate position, as well as literature data show that AMP bioavailability after *po* application in dogs was relatively low. The data for t_{max}, the high MAT value and the relatively low F_{abs} value are indicative for a comparatively slow and uncomplete AMP absorption after *po* administration. The lack of information about MAT, $t_{1/2\beta}$ and MRT after *po* AMP administration in dogs does not allow us to make any comparisons. A low bioavailability (about 18%) was reported in cats, treated orally with AMP (Mercer et al., 1977). The period where effective blood antibiotic concentrations were maintained, was not influenced negatively by FM after *iv* co-administration of AMP and FM, a fact, favourable for the maintenance of blood therapeutic concentrations. The tendency towards elevation of Vd_{area} of AMP under the influence of FM suggested that this NSAID enhanced the distribution of the antibiotic. The data for higher C_{max}, AUC and F_r could be interpreted as a trend for a higher degree of AMP absorption following *po* co-administration with FM which is not accompanied by a significant influence on $t_{1/2\beta}$.

Literature data (Baggot *et al.,* 1985) and our results indicate that in dogs, AMK was disposed rapidly and was eliminated comparatively slowly. The low values of Vd_{area}, V_c, V_t and V_{ss}, as well as the high ratios V_c/V_{ss} and $\beta.100/k_{el}$ were an evidence for the limited AMK distribution. The lack of changes in α, k_{12} and k_{21} when the combination AMK-FM was applied suggested that FM did not influence negatively the transport of AMK through membranes. The predilection of AMK for presence primarily in the central compartment (manifested by the relatively high values of $\beta.100/k_{el}$ and V_c/V_{ss} ratios) was not influenced by FM.

The comparisons of data for the drug interactions of FM with those, reported for some other NSAIDs are interesting. There are evidences that phenylbutazone and indomethacin change significantly their disposition and slow the elimination rate of aminoglycosides in horses and humans (Zarfin et al., 1985; Firth et al., 1990) and that of penicillin in cows (Hekman et al., 1982). On the other hand, it is established that paracetamol and nif-

luminic acid do not alter significantly t1/2□□and AUC of amoxicillin, cefadroxil and cefixime (Carsenti-Etesse et al., 1998). Both our results and literature data allow us to conclude that FM, by the nature of its interaction with AMP/AMK could be referred to the second cathegory NSAIDs and that there is no reason to expect uniform changes in the pharmacokinetics of antibacterial drugs under the influence of various NSAIDs.

Table 3. Doses of ampicillin sodium (mg/kg) derived from the pharmacokinetic data for amp after its single iv (n=6) and po (n=5) administration and after co-administration with flinixin meglumine (FM - 1 mg/kg) in dogs

Prepara-tion/combination and route of administration	Dosage intervals (h)										
	5 6 8										

		Cmin (□g/ml) Cmin (□g/ml) Cmin (□g/ml) Cmin (□g/ml)									
	4	0.1 0.5 1 0.1 0.5 1 0.1 0.5 1 0.1 0.5 AMP (iv) 1.3 6.3 13 2.2 11 22 3.8 18.8 37.6 10.6 52.8 AMP (iv) + FM (iv) 1.7 8.6 17 3.1 15.7 31 5.6 27.9 55.8 17.1 85.6									
AMP (po)	7.3	36.5	73	16	80	160	35	173	345	159	796
AMP (po) + FM (*iv*)	**5**	**25**	**50**	**11.7**	**58**	117	**27**	133	268	138	693

Cp_{min} - the minimum desirable serum AMP concentrations; the figures in bold are recommendable doses.

Table 4. Doses of amikacin sulfate (AMK) (mg/kg) derived from the pharmacokinetic data

The pharmacokinetic parameters of AMP and AMK, obtained in the present study on the single and combined application of antibiotics with FM and the bibliographic data about MIC (Prescott and Baggot, 1993) permitted the calculation of appropriate dose regimens (Tables 3 and 4).

On the basis of the present study, we could accept that the co-administration of FM (*iv*) and AMP (*iv* or *po*) or FM (*iv*) and AMK (*iv*) in dogs was admissible from a pharmacokinetic point of view.

ACKNOWLEDGEMENTS:

The authors acknowledge the Bulgarian office of Shering Plough and Dr. M. Toncheva for their assistance in providing Finadyne.

REFERENCES

Baggot, J. D., 1977. Principles of Drug Disposition in Domestic Animals, W. B. Saunders Co., Philadelphia, London, Toronto.

Baggot, J. D., 1984. Factors involved in the choice of routes of administration of antimicrobial drugs. *Journal of the American Veterinary Medical Association*, **185**, No 10, 1076-1082.

Baggot, D. J., G. V. Ling and R. C. Chatfield, 1985. Clinical pharmacokinetics of amikacin in dogs. *American Journal of Veterinary Research*, **46**, 1792-1796.

Bennett, J. V., J. L. Brodie and E. J. Benner, 1966. Simplified method for antibiotic assay of clinical specimens. *Applied Microbiology*., **14**, 170-177.

Cabana, E. B., L. E. Willhite and M. E. Bierwagen, 1969. Pharmacokinetic evaluation of the oral absorption of different ampicillin preparations in Beagle dogs. *Antimicrobial Agents and Chemotherapy*, 35-41.

Carsenti-Etesse H., R. Farinotti, J. Durant, P. M. Roger, F. De Salvador, E. Bernard, B. Rouveix and P. Dellamonica, 1998. Pharmacokinetic parameters and killing rates in serum of volunteers receiving amoxicillin, cefadroxil or cefixime alone or associated with niflumic acid or paracetamol. *European Journal of Drug Metabolism and Pharmacokinetics*, **3**, 357-366.

Dunkle, N. J., G. D. Bottoms, J. F. Fessler, K. Knox and O. F. Roesel, 1985. Effects of flunixin meglumine on the blood pressure and fluid compartment volume changes in ponies given endotoxin. *American Journal of Veterinary Research*, **46**, 1540-1544.

Firth, E. C., J. F. M. Nouws, W. R. Klein and F. Driessens, 1990. The effect of phenylbuthazone on the plasma disposition of penicillin G in the horse. *Journal of Veterinary Pharmacology and Therapeutics*, **13**, 179-185.

Gibaldi, M and D. Perrier, 1982. *Pharmacokinetics*, 2nd edn, Marcel Dekker, New York.

Hardie, E., G. Hardee and C. Rawlings, 1985. Pharmacokinetics of flunixin meglumine in dogs. *American Journal of Veterinary Research*, **46**, 235-237.

Hekman, P., F. M. Nouws and C. A. M. van Ginneken, 1982. Effect of Tomanol® on the pharmacokinetics and tissue distribution of penicillin G in dairy cows. *The Veterinary Quarterly*, **4**, 12-18.

Keefe, T. J. and T. A. Smith, 1977. Bioavailability of amoxicillin, ampicillin and hetacillin in the dog. *Modern Veterinary Practice*, 120-121.

Lavy E., R. Goldstein, M. Shem-Tov, A. Glickman, G. Ziv and H. Bark, 1995. Disposition kinetics of ampicillin ad-

ministered intravenously and intraosseously to canine puppies. *Journal of Veterinary Pharmacology and Therapeutics*, **18**, 379-381.

Ling, G. V. and C. J. Gilmore, 1977. Penicillin G or ampicillin for oral treatment of canine urinary tract infections. *American Journal of Veterinary Research*, **7**, 358 -362.

Mercer, D. H., R. C. Garg, J. D. Powers and T. E. Powers, 1977. Bioavailability and pharmacokinetics of several dosage forms of ampicillin in the cat. *American Journal of Veterinary Research*, **38**, 1353-1359.

Papich, G. M., 1988. Therapy of gram-positive bacterial infections. *Veterinary Clinics of North America: Small Animal Practice*, **18**, 1267-1285.

Prescott, F. J. and J. D. Baggot, 1993. Antimicrobial Therapy in Veterinary Medicine. 2nd edn. Iowa State University Press/Ames.

Rowland, M. and T. N. Tozer, 1995. Clinical Pharmacokinetics. Concepts and Applications. 3rd edn. Williams & Wilkins, Baltimore, Philadelphia, Hong Kong, London, Munich, Sydney, Tokyo.

Vonderhaar, M. and S. K. Salisbury, 1993. Gastroduodenal ulceration associated with flunixin meglumine administration in three dogs. *Journal of the American Veterinary Medical Association*, **203**, 92-95.

Watson, A. D. J., D. R. Emslie, I. C. A. Martin & J. R. Egerton, 1986. Effect of ingesta on systemic availability of penicillins administered orally in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, **9**, 140-149.

Yamaoka, K., T. Nakagawa, and T. Uno, 1978. Application of Akaike`s information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *Journal of Pharmacokinetics and Biopharmaceutics*, **6**, 165-175.

Zarfin, Y., G. Koren, D. Maresky, M. Perlman and M. D. MacLeod, 1985. Possible indomethacin-aminoglycoside interaction in preterm infants. *Journal of Pediatrics*, **106**, 511-513.

Paper received 22.11.1999; accepted for publication 22.03.2000

Correspondence: Dr. A. Haritova
Dept. Pharmacology, Toxicology and General Therapeutics,
Faculty of Veterinary Medicine,
Trakia University,
6000 Stara Zagora,
Bulgaria