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INFLUENCE OF METAMIZOLE AND DEXAMETHASONE ON AMIKACIN PHARMACOKINETICS IN DOGS

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Summary

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The pharmacokinetics of amikacin (AMK) administered intravenously and subcutaneously independently and after intramuscular administration of metamizole or dexamethasone in female dogs has been studied.

After a single *i.v.* injection of AMK, the elimination half-life ($t_{1/2\beta}$) was 1.36±0.25 h. The distribution rate constants k_{12} and k_{21} were 0.96±0.34 h^{-1} and 2.54±0.71 h^{-1}, respectively The volume of the central compartment (Vc) was 0.155±0.01 l/kg and the volume of distribution at steady-state (Vss) was 0.225±0.01 l/kg. The total body clearance was 2.10±0.19 ml/kg/min. Under the influence of metamizole the values of k_{12} and k_{21} were 3.5 and 2.5 times higher, respectively. The Vc and Vss were significantly decreased by 21.29 % and 17.33 %, respectively. When AMK was co-administered with dexamethasone, only the value of k_{el} was significantly increased two times.

After a single *s.c.* injection of AMK the $t_{1/2\beta}$ value was 1.3±0.06 h and mean absorption time (MAT) was 1.17±0.19 h. The absolute bioavailability was 107.27±14.31 %. When amikacin was administered subcutaneously following pretreatment with metamizole, there was a tendency towards higher antibiotic plasma levels. The MAT value was nearly 4 times higher and the $t_{1/2\beta}$ value was significantly higher with 30.77 %. Therefore, we assumed that the route of antibiotic administration plays a role, when these drugs were given simultaneously. The kinetic interaction between amikacin and metamizole could be of clinical significance and may require adjustment of amikacin dosage.

After subcutaneous injection of amikacin following a pretreatment of dexamethasone, the pharmacokinetics of AMK was not changed significantly.

Key words: amikacin, dexamethasone, dogs, drug interactions, metamizole, pharmacokinetics

INTRODUCTION

Aminoglycosides are frequently used to cure bacterial infections in dogs. Amikacin (AMK), a member of the aminoglycoside group, exhibits a good activity against gram-negative and some gram-positive bacteria. It inhibits or kills many aerobic gram-negative bacteria such as *E. coli*, *Enterobacter spp.*, *Klebsiella spp., Proteus spp*., *Salmonella spp*., *Actinobacillus spp*. and others (Prescott and Baggot, 1993).

When bacterial infection is the cause of an inflammatory reaction, NSAIDs and steroid anti-inflammatory agents are commonly administered simultaneously with appropriate antibacterial agents. The pharmacologic effects of NSAIDs include analgesia, antipyresis, and control of in-

flammation (Nolan, 2000). Viral infections accompanied by secondary bacterial infection have been also treated with NSAIDs and antibiotics. In spite of the frequent clinical use only limited data about the pharmacokinetic interaction of anti-inflammatory agents and antibiotics, including amikacin, are available. Phenylbutazone induced changes to the rate and extent of distribution and elimination of gentamicin in horses (Whittem et al., 1996). Scheld & Brodeur (1983) reported that methylprednisolone decreases gentamicin concentrations in cerebrospinal fluid in rabbits. When AMK was co-administered with metamizole, there was a tendency towards prolongation of the elimination half-life of AMK in rabbits, but after the treatment with dexamethasone a tendency towards decrease of this parameter was determined (Haritova and Atanassova, 1999). Besides these data, little is known about changes of aminoglycoside pharmacokinetics due to simultaneous administration of anti-inflammatory drugs.

The aim of the present study was to investigate the influence of metamizole or dexamethasone, intramuscularly administered on the amikacin pharmacokinetics in dogs.

MATERIALS AND METHODS

Animals

Six crossbred female dogs, 1-4 years old and with body weight of 16.04±1.76 kg were used for this study. They were determined clinically healthy by means of daily observation (for 20 days), physical examination and complete haemogram. Animal care and handling were in accordance with the provisions of the European Community, adopted by the Bulgarian Government.

Drugs

The following drugs were used in the experiments: amikacin sulfate (Amikacin, 5 % injectable solution, So-pharma); metamizole (Analgin, 50 % injectable solution, Sopharma) and dexamethasone (Dexamethasone, 0.2 % injectable solution, Veterin).

Treatment

The intravenous (*i.v.*) and subcutaneous (*s.c.*) doses of AMK were 5 mg/kg b.w.. All dogs were included in six subsequent experiments:

Experiment I: *i.v.* treatment (*v. cephalica*) with AMK.

Experiment II: intramuscular (*i.m.*) treatment with 30 mg/kg b.w. metamizole followed 30 min later by a single *i.v.* dose of AMK.

Experiment III: *i.m.* treatment with dexamethasone at a dose rate of 100 μg/kg b.w., applied twice at an interval of 24 h followed by an *i.v.* dose of AMK 30 minutes after the second application of dexametasone.

Experiment IV: *s.c.* treatment with AMK.

Experiment V: *i.m.* treatment with 30 mg/kg b.w. metamizole followed 30 min later by a single *s.c.* dose of AMK.

Experiment VI: *i.m.* application of dexamethasone at a dose rate of 100 μg/kg, applied twice at an interval of 24 h followed by a *s.c.* dose of AMK 30 minutes after the second application of dexamethasone.

Each experiment was followed by a 28 days washout period.

Sampling

When the antibiotic was given *intravenously*, blood samples were collected from the *v. cephalica* (the opposite vein, that was not used for AMK administration), using an intravenous catheter 22G

(Helm Pharmaceuticals GmbH, Germany). Samples were collected before each treatment with AMK and at 0.083; 0.25; 0.5; 1; 2; 4; 5; 6; 8 and 10 hrs after the administration. After *s.c.* administration, blood samples were collected in sterile heparin-coated plastic tubes from *v. cephalica* before each AMK treatment and at 0.25; 0.5; 1; 2; 4; 5; 6 and 8 hrs after the application.

The blood was centrifuged at 1500 × g for 15 min. The plasma samples were kept in plastic tubes at - 20^0C until analysis. The drug analysis was carried out one day after sampling.

Drug analysis

Plasma concentrations of AMK were determined by using *Bac. mycoides HB$_2$* as test microorganism (Bennet et al., 1966). The standard solutions were prepared in plasma obtained from untreated dogs. The limit of quantitation was 0.18 μg AMK/ml plasma.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed using the two-compartment open model for the data obtained after *i.v.* administration according to the equation

$Cp = Ae^{-\alpha t} + Be^{-\beta t}$, where:

Cp – plasma AMK concentration at time t, A – zero-time concentration intercept of the distribution curve; α - hybrid rate constant for the distribution phase; B - zero-time concentration intercept of the elimination curve; β- hybrid rate constant for the elimination phase; e = base of natural logarithm.

The most appropriate model was chosen according to the Akaike's information criterion. Non compartmental analysis based on statistical moment theory was also performed for the data obtained after *i.v.* and *s.c.* injection. The relevant pharmacokinetic indices are shown in Table 1. The values of area under plasma concentration time-curve (AUC) and the area under the moment curve (AUMC) were calculated by using linear trapezoidal rule with extrapolation to infinity. When AMK was injected *s.c.*, the mean absorption time (MAT) value was calculated according to the equation $MAT=MRT_{s.c.}-MRT_{i.v.}$, where $MRT_{s.c}$ and $MRT_{i.v.}$ are the MRT of drug after *s.c.* or *i.v.* administration, respectively.

The absolute bioavailability was calculated as $AUC_{s.c.}/AUC_{i.v.}$, where $AUC_{s.c.}$ or $AUC_{i.v.}$ are the AUC of drug after *s.c.* or *i.v.* administration, respectively. The relative bioavailability (Fr) was calculated according to the equation: $Fr=AUC_{s.c.\ \text{coadministration}} / AUC_{s.c.\ \text{single administration}}$.

The *i.v.* maintenance dose was determined according to the equation:

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

Cp_{min} = minimum inhibitory concentrations = MIC; Vd_{area} = area volume of distribution; e = the base of natural logarithm; τ = dosage interval; β= hybrid rate constant for the elimination phase (Baggot, 1977).

The *s.c.* maintenance dose was determined according to the equation:

$Bapp = Cp_{min}.(1-e^{-\beta \cdot \tau}) / e^{-\beta \cdot \tau}$, where:

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

The doses and dose intervals were considered with the acceptable fluctuations of plasma AMK levels.

Statistical analysis

Pharmacokinetic parameters are presented as mean ± SEM. For half-life values in

serum, harmonic means and their SD were computed. The statistically significant differences between pharmacokinetic parameters following the single administration of AMK and its co-administration with metamizole or dexamethasone were determined using the Student's t-test. They were calculated by using computer program Statistica (StatSoft, 1991). P values < 0.05 were considered significant.

RESULTS

AMK concentration-time profile is presented in Fig. 1. After a single *i.v.* injection of the antibiotic in dogs, the maximum AMK plasma levels were 26.95±1.61 μg/ml at 0.083 hrs. Thereafter, the AMK plasma levels decreased slowly towards 0.48±0.07 μg/ml at 8 hrs. Ten hours after injection, AMK was not found in plasma. The pharmacokinetic behavior of AMK was best described by two-compartment open model.

The elimination half-life was 1.36±0.25 h. The parameters, describing AMK distribution were as follows: volume of distribution Vd_{area} = 0.298±0.06 l/kg and volume of distribution at steady state, Vss 0.23±0.01 l/kg. The value of k_{12} and k_{21} were 0.96±0.34 h^{-1} and 2.54±0.71 h^{-1}, respectively. The value of total body clearance was 2.10±0.19 ml/kg/min. The ratio of β to k_{el}, was 60.83 % (Table 1).

After administration of AMK to animals pretreated with metamizole, changes in the maximum plasma antibiotic levels 39.94±1.96 μg/ml were found at 0.083 hrs (Fig. 1). There was a tendency towards decreasing the values of $t_{1/2\alpha}$ (0.1±0.03 h) and $t_{1/2\beta}$ (1.14±0.098 h). The values of k_{12} (3.34±0.76 h^{-1}) and k_{21} (6.58±1.64 h^{-1}) were 3.5 and 2.5 times higher, respectively. The value of distribution in the central compartment (Vc=0.122±0.007 l/kg) and at steady state (Vss=0.186±0.004 l/kg) were significantly decreased by 21.29 % and 17.33 %, respectively. The other pharmacokinetic parameters were not significantly changed. The ratio of β.100/k_{el}, was 61.36 (Table 1).

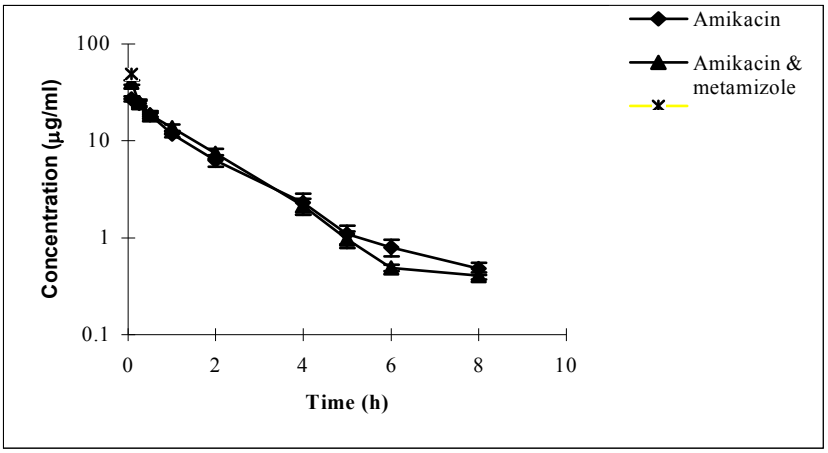

Fig. 1. Mean ± SEM plasma concentrations of amikacin in dogs (n=6) after *i.v.* application of 5 mg/kg b.w.- independently and after i.m. administration of metamizole at 30 mg/kg b.w. * Statistically significant difference at p<0.05 level.

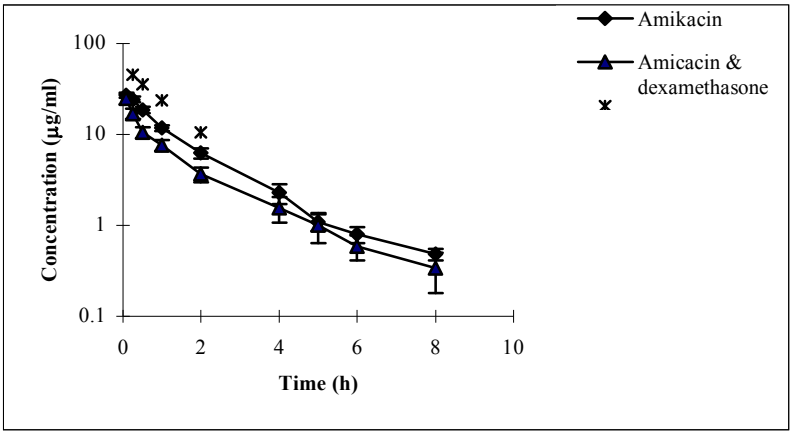

Fig. 2. Mean ± SEM plasma concentrations of amikacin in dogs after *i.v.* application of 5 mg/kg b.w. - independently and after *i.m.* administration of dexamethasone at 100 µg/kg b.w. * Statistically significant difference at $p<0.05$ level.

When amikacin was administered to animals pretreated with dexamethasone, the antibiotic plasma levels were significantly lower from 0.25 hrs (16.90±2.15 µg/ml) to 2 hrs (3.64±0.68 µg/ml) *post injectionem*. Thereafter, only a tendency towards decreased plasma AMK concentrations was observed (Fig. 2). Pharmacokinetic parameters are shown in Table 1. The AUC value of 26.98 ± 4.19 µg.h/ml was lower than in AMK treated animals. The value of $t_{1/2\alpha}$ (0.23±0.08 h) decreased by 23.08 %, whereas that of $t_{1/2\beta}$ (1.57±0.15 h) increased by 15.44 %. The total body clearance of 3.58±0.68 ml/kg/min was insignificantly higher in this group The ratio of β.100 to k_{el}, was 33.28 (Table 1).

After a single *s.c.* administration of AMK to dogs, the plasma antibiotic level at 0.25 hrs *post injectionem* was 15.13±1.86 µg/ml. The AMK levels declined rapidly towards 0.39±0.017 µg/ml at 8 hrs. The C_{max} value of 17.75±1.41 µg/ml was achieved at t_{max} of 0.46±0.04 h. The values of $t_{1/2\beta}$ and MRT were 1.30±0.06 h and 1.94±0.18 h, respectively. The value of MAT was 0.30±0.25 h. The absolute bioavailability was calculated to be 107.27±14.31 % (Table 1).

After metamizole pre-treatment the AMK plasma levels were insignificantly lower from 0.25 hrs (10.48±1.17 µg/ml) to 1 h (13.34±0.84 µg/ml) p.a. Thereafter, they tended to be higher than those produced by the single AMK administration (Fig. 3). The values of MAT (1.17±0.19 h) and $t_{1/2\beta}$ (1.70±0.14 h) were higher in comparison to a single injection of AMK. There was a tendency towards reduced values for C_{max} (14.15±1.02 µg/ml). The values of the absolute and relative bioavailability were 110.44±11.9 % and 114.0±8.8 %, respectively (Table 1).

The plasma AMK levels were not changed under influence of dexamethasone (Fig. 4) and thus, the pharmacokinetic parameters were not changed significantly, too.

Table 1. Pharmacokinetic parameters of amikacin in plasma administered *i.v.* or *s.c.* to dogs (n = 6) following *i.m.* administration of metamizole (30 mg/kg b.w.) or dexamethasone (100 μg/kg b.w. twice with an interval of 24 hrs), mean±SEM

Parameters	Amikacin	Amikacin and metamizole	Amikacin and dexamethasone
Two compartmental analysis, *i.v.*			
A (μg/ml)	16.39±3.84	17.63±2.55	24.28±6.7
α (h^{-1})	3.84±0.92	10.32±2.22*	6.75±2.66
$t_{1/2\alpha}$ (h)	0.299±0.11	0.1±0.03	0.23±0.08
B (μg/ml)	16.52±3.51	24.07±0.85	11.69±4.52
β (h^{-1})	0.511±0.09	0.632±0.06	0.466±0.05
$t_{1/2\beta}$ (h)	1.36±0.25	1.14±0.098	1.57±0.15
$t_{1/2\beta}^{\#}$ (h)	1.21±0.42	1.09±0.28	1.49±0.39
k_{12} (h^{-1})	0.96±0.34	3.34±0.76*	3.40±1.99
k_{21} (h^{-1})	2.54±0.71	6.58±1.64*	1.81±0.49
k_{el} (h^{-1})	0.84±0.07	1.03±0.11	1.40±0.19*
β.100/k_{el}	60.83	61.36	33.28
Vd_{area} (l/kg)	0.298±0.06	0.196±0.005	0.447±0.1
Vc (l/kg)	0.155±0.01	0.122±0.007*	0.16±0.02
Vt (l/kg)	0.070±0.01	0.129±0.06	0.208±0.08
Vss (l/kg)	0.225±0.01	0.186±0.004*	0.373±0.08
MRT (h)	1.83±0.21	1.58±0.12	1.79±0.23
Cl (ml/kg/min)	2.17±0.19	2.07±0.22	3.61±0.64
AUC (μg/ml.h)	40.17±3.80	42.25±3.74	34.12±10.45
Noncompartmental analysis, *i.v.*			
Vd_{area} (l/kg)	0.241±0.016	0.198±0.01	0.40±0.06*
Vss (l/kg)	0.199±0.008	0.17±0.009*	0.34±0.07
MRT (h)	1.64±0.140	1.49±0.070	1.64±0.20
AUC (μg/ml.h)	41.50±3.910	44.54±3.35	26.98±4.19*
Cl (ml/kg/min)	2.10±0.190	1.83±0.210	3.58±0.68
Noncompartmental analysis, *s.c.*			
β (h^{-1})	0.538±0.02	0.43±0.03*	0.547±0.03
$t_{1/2\beta}$ (h)	1.30±0.06	1.70±0.14*	1.28±0.076
$t_{1/2\beta}^{\#}$ (h)	1.29±0.13	1.65±0.26	1.26±0.19
C_{max} (μg/ml)	17.75±1.41	14.15±1.02	16.93±1.18
t_{max} (h)	0.46±0.04	0.667±0.11	0.625±0.13
MRT (h)	1.94±0.18	2.66±0.213*	2.17±0.13
MAT (h)	0.30±0.25	1.17±0.19*	0.53±0.23
AUC (μg/ml.h)	42.38±2.94	48.32±4.26	45.98±1.33
Fabs (%)	107.27±14.31	110.44±11.99	194.95±33.41*
Fr (%)		114.0±8.80	04.83±9.91

* statistically significant difference at $p<0.05$ level; # - harmonic mean presented as mean±SD; A-zero-time concentration intercept of the distribution curve; B-zero-time concentration intercept of the elimination curve; α - hybrid rate constant for the distribution phase; β - hybrid rate constant for the elimination phase; 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; $t_{1/2\alpha}$ - distribution phase half-life time; $t_{1/2\beta}$ - elimination phase half-life time; C_{max} - peak drug concentration; t_{max} - time of C_{max} ; AUC - area under the concentration vs. time curve; AUMC - area under the first moment curve; Vdarea, Vc, Vt, Vss - area volume of distribution, volume of the central and the peripheral compartment, volume of distribution at steady-state respectively; MRT - mean residence time, MAT - mean absorption time; Cl_B - total body clearance;F_{abs}% -absolute bioavailability; F_r% - relative bioavailability.

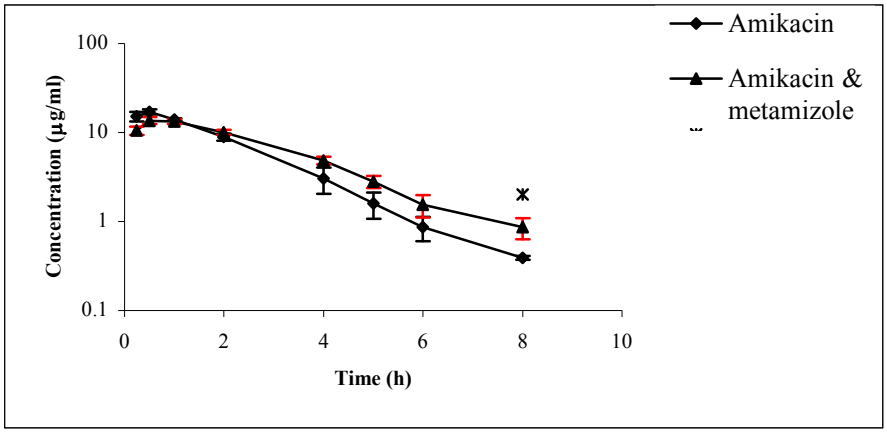

Fig. 3. Mean ± SEM plasma concentrations of amikacin in dogs (n = 6) after *s.c.* application of 5 mg/kg b.w. - independently and after *i.m.* administration of metamizole at 30 mg/kg b.w.

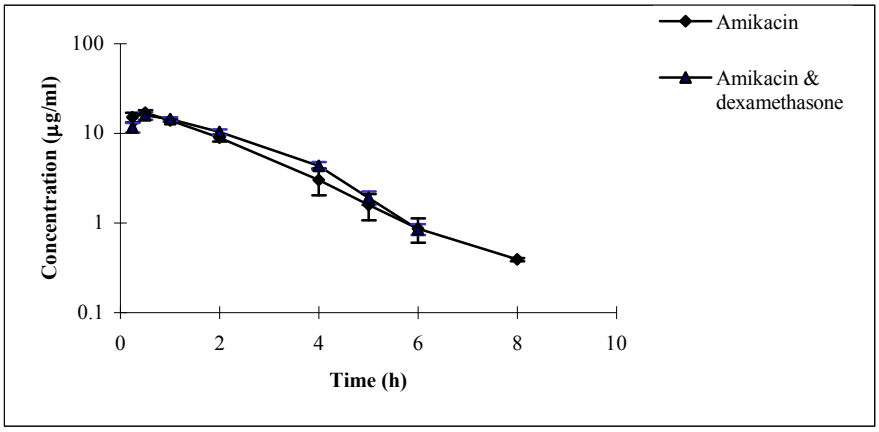

Fig. 4. Mean ± SEM plasma concentrations of amikacin in dogs (n = 6) after *s.c.* application of 5 mg/kg b.w.- independently and after *i.m.* administration of dexamethasone at 100 µg/kg b.w. (twice with an interval of 24 hrs).

There was only tendency towards an increased t_{max} value to 0.625±0.13 h and an increased MAT value to 0.53±0.23 h. The absolute and relative bioavailability was 194.95±33.41 % and 104.83±9.91 %, respectively (Table 1).

DISCUSSION

The minimum inhibitory concentrations (MIC) of amikacin against susceptible bacteria vary between 1 to 4 µg/ml (Navashin & Fomina, 1982; Orsini *et al.,* 1985; Prescott and Baggot, 1993). The

AMK plasma levels after a single *i.v* or *s.c.* injection in dogs in our study were thus effective against most AMK sensitive microorganisms up to 5 hours. Under the influence of metamizole and dexamethasone the plasma AMK levels were above the MIC values between 5 or 6 hours.

AMK pharmacokinetics after single *i.v.* administration in dogs was characterized with rapid distribution and slow elimination. The values for $t_{1/2\beta}$ of 1.07 h, for Cl_B of 2.82 ml/kg/min and for Vd_{area} of 0.26 l/kg, as reported by Baggot *et al.* (1985) are similar to that found in this study. The rate of AMK distribution from the central to the peripheral compartment is 2.5 times slower than the rate of AMK distribution from the peripheral to the central compartment. The low values of AMK volume of distributions suggest a low degree of distribution, a fact which is supported by the Vc:Vss ratio - 0.69. Only 31 % of AMK were distributed into the peripheral compartment and 60.83% was available for elimination from the central compartment. The probable reason for the relatively fast AMK elimination, despite the low Cl_B, was the high AMK presence in the central compartment.

When AMK was administered intravenously to animals pretreated with metamizole there was an increase in the rates of AMK distribution from the central to the peripheral compartment and backwards. In spite of significantly decreased Vc and Vss, their ratio was decreased only to 0.66. These data allow us to conclude that metamizole can influence the extent but not the pattern of distribution of AMK.

The data for the changes of AMK pharmacokinetics under influence of metamizole are similar with the data, obtained after comparable studies on gentamicin and phenylbutazone. Phenylbutazone induced a 49 % increase of k_{21} and increased the rate of gentamicin return to the central compartment. In addition, there was a trend towards an increase in k_{12} in horses. The Vd_{area} was reduced by 26% (Whittem *et al.,* 1996). Such changes were also found after co-administration of phenylbutazone and sulphadimidine in bufalo calves (Balakrishnarao & Narayana, 1990). According to Hekman *et al.* (1982), phenylbutazone decreases Vss of simultaneously administered penicillin in cows, the tendency which was also determined for metamizole in our study. Interactions between gentamicin and indomethacin have also been described in humans, and it was suggested that the anti-inflammatory agent reduces the glomerular filtration rate, the rate of urine flow and thus the excretion of the water and electrolytes (Zarfin et al*.,* 1985). When AMK was administered simultaneously with indomethacin in humans, increased plasma AMK levels were observed, which were attributed to a reduction in the excretion of AMK (Zarfin et al., 1985). However, other data report the absence of changes in $t_{1/2\beta}$ and AUC for amoxycillin, cefadroxil and cefixime after co-administration with paracetamol and niflumic acid (Carsenthi-Etesse et al., 1998). In our study metamizole did not change significantly these parameters of AMK. These differences are indicative for the absence of identical changes in the pharmacokinetics of antibiotics when co-administered with NSAIDs.

After *i.v.* administration of AMK to dogs pretreated with dexamethasone, the amount of AMK in the central compartment in the post-distributional phase was decreased by 50%. The lower Vc:Vss ratio of 0.43 supported the decrease of AMK in the central compartment.

Table 2. Doses of AMK (mg/kg) derived from the data for amikacin after single *i.v.* and *s.c.* administration and after pretreatment with metamizole (30 mg/kg b.w.) or dexamethasone (100 μg/kg b.w.) in dogs (n=6)

Preparation/combination and route of administration	Cp_{min} (μg/ml)	Dosage intervals (h)		
		4	6	8
AMK (*i.v.*)	1	**2.00**	**6.09**	17.47
	2	**4.00**	12.19	34.94
	4	**8.01**	24.38	69.88
AMK (*i.v.*)+ M (i.m.)	1	**2.26**	8.50	30.57
	2	**4.52**	16.99	61.14
	4	9.04	33.98	122.30
AMK (*i.v.*) + D (i.m.)	1	**2.44**	**6.87**	18.14
	2	**4.87**	**13.75**	36.29
	4	**9.74**	27.50	72.59
AMK (*s.c.*)	1	**1.69**	**5.37**	16.20
	2	**3.37**	10.70	33.40
	4	**6.74**	21.50	64.70
AMK (*s.c.*) + M (i.m.)	1	**1.09**	**2.89**	**7.16**
	2	**2.17**	**5.79**	14.30
	4	**4.35**	11.60	28.60
AMK (*s.c.*) + D (i.m.)	1	**1.45**	**4.71**	14.42
	2	**2.91**	9.42	28.80
	4	**5.82**	18.80	57.70

Cp_{min} - the minimum desirable serum AMK concentrations; M - metamizole;D - dexamethasone. Note: the doses in bold are provided plasma concentrations under toxic levels of 40 μg/ml. They were determined according to the equation: $C_{max}=D/Vd_{area}.(1 - e^{-\beta\tau})$.

The data for the possibility of glucocorticoids to increase extracellular fluid, enhance the glomerular filtration rate and increase the urine volume (Ferguson, 1985; Nakamoto, 1992), are the probable reason for the slight changes in Cl_B. However, it is obvious that dexamethasone did not change the water balance and thus the elimination of AMK in the dogs in our study (Ferguson, 1985).

The t_{max} values of AMK after a single *s.c.* administration in dogs in our study are similar to that reported by other authors in dogs and cats: from 0.5 h to 0.75 h (Cabana & Taggart, 1973; Jernigan et al., 1988). These data and the low value of MAT are indicative for a rapid absorption. The data reported by Baggot et al. (1985) for $t_{1/2\beta}$ (1.67 h) after a single *s.c.* injection of AMK in dogs are very similar to that found in this study (1.30 h). The high bioavailability of 107.27±14.31 % in dogs is typical for AMK and corresponded with an F_{abs} of 123 % in cats after *s.c.* injection (Jernigan *et al.,* 1988) and F_{abs} of 106.82 % in goats (Uppal *et al.,* 1997). Therefore, we may assume that after *s.c.* AMK administration, the absorption is complete and fast. The lack of significant differences in $t_{1/2\beta}$ values after

i.v. and *s.c.* injection of AMK, show that this parameter is not dependent on the route of administration.

After *s.c.* injection of AMK to dogs pretreated with metamizole, the elimination of the antibiotic was slower and this change was not in conformity with data after *i.v.* AMK administration. The absorption was delayed, too. The C_{max} was insignificantly lower and was achieved later. The higher value of Fr allows us to assume that the pointed changes are not related to a decrease in the extent of AMK absorption.

Similarly, we could interpret the changes in Fr after *s.c.* AMK administration under influence of dexamethasone. Therefore, it could be assumed that *s.c.* injection is a convenient route for AMK administration in the practice, including after pretreatment with metamizole and dexamethasone.

It is known that when determining dosage regimens in order to provide effective treatment with bactericidal antibiotics, it is not necessary that their blood levels exceed continuously the minimal inhibitory concentration for the infecting organism (McClure and Rosin, 1998). The therapeutic efficacy is also determined by the post-antibiotic effect. The pharmacokinetic parameters of AMK obtained in our studies after its co-administration with metamizole and dexamethasone in dogs, enabled us to calculate the respective adjusted dosage regimens (Table 2), in accordance with the considerations mentioned above. The final proof of effective plasma concentrations of an antibiotic however resides in its clinical effectiveness. Therefore, calculated dose regimens for a co-administration of AMK and metamizole are intended only as guidelines, suggesting how to change the dose and dose intervals.

On the basis of the obtained data we may conclude that there are differences in drug interaction between AMK and metamizole and between AMK and dexamethasone in dogs. After *s.c.* AMK injection together with metamizole the time for absorption and elimination was increased. This fact would allow the use of lower doses of AMK in this combination. Finally, the obtained data also allow to assume that the studied combinations are admissible from pharmacokinetical point of view. At the same time, it is important to take into consideration that our results are obtained in healthy animals. Pathological conditions, such as impaired renal function, would alter the kinetics of tested drugs more significantly that the described co-medication. In such cases, there is, therefore, a need for additional information about modified pharmacokinetic parameters in order to adjust the dosage regimen.

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