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Pharmacokinetics of oleandomycin administered alone and after oral ascorbic acid in three bird species

Anelia Milanova Haritova*, and Lubomir Dimitrov Lashev

Department of Pharmacology, Toxicology and Therapeutics, Faculty of Veterinary Medicine, Thrakia University, Stara Zagora, Bulgaria

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ABSTRACT

The influence of ascorbic acid administration via drinking water at a dose of 15 mg/l over a period of 7 days on the pharmacokinetics of oleandomycin in chickens, musk ducks and Japanese quails was investigated. After ascorbic acid oleandomycin elimination, half-life was longer. Oleandomycin bioavailability in chickens and quails after *per os* application was increased with ascorbic acid. Interspecies differences in oleandomycin body disposition were observed. Lower elimination rate constants were obtained in the musk ducks in comparison with two other species. The volume of distribution (V_{ss}) was larger in quails. In conclusion, ascorbic acid did not change oleandomycin disposition significantly in the treated birds.

Key words: oleandomycin, pharmacokinetics, ascorbic acid, interaction, birds

Introduction

Oleandomycin (OLD) is a widely used macrolide antibiotic in veterinary medicine. It is effective against Gram-positive microorganisms but also against some Gram-negative strains, for example *Pasteurella* spp. (PATHANASOPHON et al., 1990) Data on its pharmacokinetics in domestic

* Contact address:
Dr. Anelia Haritova, Department of Pharmacology, Toxicology and Therapeutics, Faculty of Veterinary Medicine, Thrakia University, 6000 Stara Zagora, Bulgaria, Phone: 359 042 7 40 67; E-mail: aneliah@sz.inetg.bg

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animal species are limited. Interspecies differences in chickens, pigeons, ducks, mice, rats and dogs were reported. In bird species longer elimination half-lives ($t_{1/2\beta}$) and higher values of volume of distribution (V_{ss}) were found (DUTHU, 1985; LASHEV et al., 1999).

In bird farms, the drug combinations are often used. In these cases drug interactions may occur. Such interactions have been described for chickens (HEGEROVA and SIMUNEK, 1988; LASHEV, 1998; MOUTAFCHIEVA, 1989; RAMADAN et al., 1992). For example, the coccidiostatics and the nutritive antibiotics may significantly alter the pharmacokinetics of several antibacterial drugs (tylosin, sulfadimidine and apramycin) in the case of simultaneous administration. The simultaneous administration of antibiotics and vitamins is routinely used. Ascorbic acid influences metabolic pathways in the organism and may thus affect oleandomycin body disposition (SHARMANOV, 1979).

The aim of the present study was to investigate the influence of ascorbic acid on oleandomycin pharmacokinetics in chickens, musk ducks and Japanese quails.

Materials and methods

Animals. Experiments were carried out on twelve 8-month-old crossbreed chickens (*Gallus domesticus*) of both sexes, weighing 1.12 ± 0.08 kg; on 5 musk ducks (*Cairina moschata*), both sexes, one-year-old and weighing 2.56 ± 0.43 kg, and on 10 Japanese quails (*Coturnix coturnix japonica*) both sexes, weighing 0.129 ± 0.007 kg. Chickens and quails were kept in cages (six birds in a cage) and given free access to food (commercial food for chickens) and water. The ducks were housed in an aviary and fed a commercial diet and provided with water *ad libitum*.

Experimental design. In the first series of experiments 6 chickens, 5 quails and all musk ducks received intravenously (i.v.) oleandomycin phosphate (OLD) as water solutions via the cutaneous ulnar vein. Chickens and musk ducks were administered 15 mg/kg, and quails 30 mg/kg in solutions of 1.5% and 7.5%, respectively. Immediately prior to drug administration and at different intervals thereafter (0.083, 0.25, 0.5, 1, 2, 3, 4, 5, 6 and 7 hours for chickens and ducks and 0.25, 0.5, 1, 2, 3 and 4

hours for quails), blood samples were collected via the contralateral vein. The volume of each sample was 0.5 ml.

Two days later, all birds received ascorbic acid (AA) with drinking water at a dose of 0.15 mg/l for 7 days. On day 8 the procedure, including intravenous administration of oleandomycin and blood samples collections, was repeated.

In the second series of experiments, 6 chickens and 5 quails were treated orally (p.o.) with oleandomycin phosphate at a dose of 40 mg/kg. The first administration was given without AA and the second after 7 days AA. Blood samples were collected prior to 0.5, 1, 2, 3, 4, 5 and 7 hours (chickens), 0.5, 2, 4 and 5 hours (quails) after treatment.

Blood samples were placed in plastic tubes (without any anticoagulant) and were allowed to clot. Serum was separated, removed and frozen at -18 ^{0}C within 4 hours of collection. Assays were performed within 24 hours of sample collection.

Drug assay. OLD concentrations were assayed microbiologically by the agar diffusion method using *Bacillus mycoides* HB_2 as test microorganism, and standard solutions of the substance in adequate bird serum as a reference. The detection limit of the assay was 0.15 μg/ml. The response of oleandomycin was linear over the range of concentrations between 0.15-10 μg/ml, and mean correlation coefficient (r) of the standard curves was 0.9917 ± 0.0016.

Data analysis. Serum concentrations of OLD after i.v. administration for each bird were analyzed using a computer program. Following i.v. administration the disposition curves, which express the decline in serum drug concentrations of all of ducks as a function of time, was described by biexponential expressions: $Cp = A.e^{-\alpha.t}+B.e^{-\beta.t}$

Cp = Drug concentrations at time t

A = Intercept of distribution line with the concentration axis

B = Intercept of elimination line with the concentration axis

a = Distribution rate constant

b = Elimination rate constant

e = Base of natural logarithm (BAGGOT, 1977).

Chickens and quails showed monoexponential or biexponential dependence of the blood serum levels on the time. This is why the pharmacokinetic parameters of the chickens and quails were calculated using only the non-compartmental model. The most appropriate model was chosen by examining values of the Akaike's information criterion. Pharmacokinetic data after p.o. administration were calculated using non-compartimental analysis.

Absolute bioavailability (F_{abs}%) and relative bioavailability (F_r%) were calculated according to the formulas:

$F_{abs}\% = (AUC_{i.m.} \times D_{i.v} \times 100) / (AUC_{i.v.} \times D_{i.m.})$ and

$F_r\% = AUC_{\text{i.m. coadministration}} \times 100 / AUC_{\text{i.m. single administration}}$

The results obtained were statistically analyzed by using Student's *t*-test and Mann Whithney U test.

Results

The i.v. and p.o. introduction of OLD after AA was not followed by any detectable toxic reactions in the treated birds.

Determined OLD serum concentrations in chickens after its single i.v. administration were found until the 4th hour. After this time no detectable levels were found. OLD serum concentrations after pre-treatment with ascorbic acid were significantly lower at 0.25 h, and higher at 4 h after injection (Fig. 2). The pharmacokinetic parameters calculated are presented in Table 1. Retarded elimination and higher values of $t_{1/2\beta}$ were recognised. The AUMC, the MRT and volume of distribution (Vd_{ss}) values were significantly increased, whereas total body clearance (Cl_B) was insignificantly decreased.

No statistically significant differences between the pharmacokinetic parameters in quails before and after AA treatment were found (Fig. 3 and Table 1). Tendencies of the differences between two groups found are similar to those found in chickens (lower AUC and higher $t_{1/2\beta}$, MRT and Vd_{ss} values were observed).

OLD could be detected until the 5th hour after injection in ducks (Fig. 1). All individuals were characterized by a two-compartment open model.

Table 1. Pharmacokinetic parameters of oleandomycin in chickens and quails after i.v. administration alone and after ascorbic acid (x ± SEM)

Parameters	Chickens (15 mg/kg)		Japanese quails (30 mg/kg)	
	OLD	OLD + AA	OLD	OLD + AA
B (μg/ml)	1.7 ± 0.2	1.53 ± 0.32	3.23 ± 0.55	4.59 ± 1.68
β (h^{-1})	0.533 ± 0.04	0.386 ± 0.05^{+}*	0.593 ± 0.07	0.597 ± 0.09
$t_{1/2\beta}$ (h)	1.35 ± 0.13	1.53 ± 0.32^{+}*	1.25 ± 0.18	1.31 ± 0.24
MRT (h)	1.36 ± 0.06	2.08 ± 0.22^{+}*	1.09 ± 0.11	1.28 ± 0.06
V_d (l/kg)	6.43 ± 1.8	8.14 ± 0.85	5.58 ± 1.19	6.89 ± 1.77
V_{ss} (l/kg)	4.44 ± 0.35	6.07 ± 0.64^{+}*	3.3 ± 0.53	4.44 ± 0.55
Cl_B (ml/min/kg)	54.18 ± 2.49	49.08 ± 2.83	50.28 ± 4.44	57.44 ± 5.75
AUC (μgxh/ml)	4.67 ± 0.24	5.17 ± 0.28	10.29 ± 0.99	9.09 ± 0.98
AUMC(μgxh^2/ml)	6.31 ± 0.3	10.84 ± 1.48^{+}*	11.04 ± 1.27	11.52 ± 1.18

* Statistically significant at P≤0.05 up to Student's *t*-test; $^{+}$ Statistically significant at P≤0.05 up to Mann Whitney U test;
β - terminal (elimination) rate constant; $t_{1/2\beta}$ - terminal elimination half-life; AUC - area under the concentration-time curves; V_d area, V_{ss} - apparent volume of distribution, steady-state volume of distribution, respectively; MRT - mean residence time, Cl_B - total body clearance, AUMC - area under the first moment curve, MRT - mean residence time

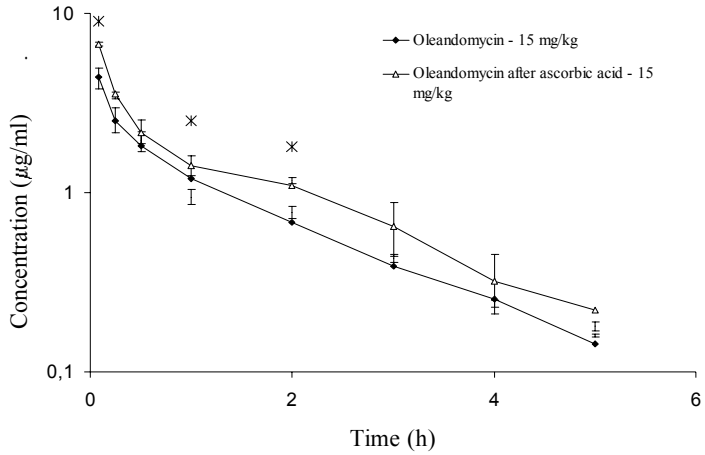

Fig. 1. Serum concentrations (mean ± SEM) of oleandomycin after intravenous administration alone and after oral administration of ascorbic acid for 7 days at a dose rate of 0.15 mg/l water in musk ducks (n = 5). * Statistically significant at P≤0.05 up to Student's *t*-test

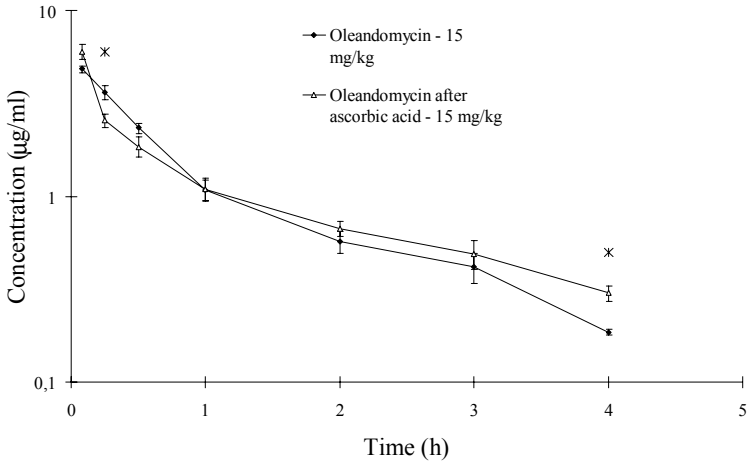

Fig. 2. Serum concentrations (mean ± SEM) of oleandomycin after intravenous administration alone and after oral administration of ascorbic acid for 7 days at a dose rate of 0.15 µg/l water in chickens (n = 6), * Statistically significant at P≤0.05 up to Student's *t*-test

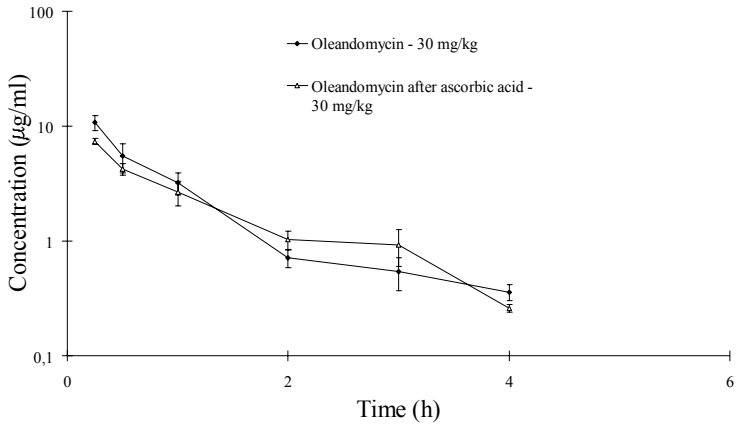

Fig. 3. Serum concentrations (mean ± SEM) of oleandomycin after intravenous administration alone and after oral administration of ascorbic acid for 7 days at a dose rate of 0.15 mg/l water in Japanese quails (n = 5)

Table 2. Pharmacokinetic parameters of oleandomycin in musk ducks after i.v. administration (x ± SEM)

Parameters	Musk ducks (15 mg/kg)	
	OLD	OLD + AA
A (μg/ml)	4.86 ± 0.78	7.81 ± 0.36*$^{+}$
B (μg/ml)	1.71 ± 0.36	2.15 ± 0.355
α (h^{-1})	9.61 ± 3.06	6.83 ± 1.04
β (h^{-1})	0.45 ± 0.08	0.442 ± 0.08
k_{21} (h^{-1})	2.88 ± 0.97	1.86 ± 0.41
k_{12} (h^{-1})	5.66 ± 1.99	3.72 ± 0.62
$t_{1/2\alpha}$ (h)	0.16 ± 0.07	0.11 ± 0.02
$t_{1/2\beta}$ (h)	1.76 ± 0.32	1.91 ± 0.5
MRT (h)	2.02 ± 0.24	2.24 ± 0.63
V_d (l/kg)	8.41 ± 1.22	5.99 ± 0.74
V_c (l/kg)	2.54 ± 0.39	1.49 ± 0.06*$^{+}$
V_3 (l/kg)	4.24 ± 0.53	3.27 ± 0.44
V_{ss} (l/kg)	6.78 ± 0.75	4.77 ± 0.47^{+}
Cl_B (ml/min/kg)	57.35 ± 5.1	41.68 ± 6.75
AUC (μg/ml.h)	4.51 ± 0.43	6.81 ± 1.3

* Statistically significant at P≤0.05 up to Student's *t*-test; $^{+}$ Statistically significant at P≤0.05 up to Mann Whitney U test

α - distribution rate constant; β - terminal (elimination) rate constant; k_{el} - elimination rate constant from central compartment; k_{12}, k_{21} - the distribution rate constants from central to peripheral compartment and back; $t_{1/2\alpha}$ - distribution half-life; $t_{1/2\beta}$ - terminal elimination half-life; AUC - area under the concentration-time curves; V_d area, V_c, V_p, V_{ss} - apparent volume of distribution, the distribution volume of central and peripheral compartment, steady-state volume of distribution, respectively; MRT - mean residence time, Cl_B - total body clearance

These birds had larger values of $t_{1/2\beta}$ in comparison to the other species. After AA pre-treatment the distribution rate constant was not affected; elimination half-life was slightly longer; the Vd_a, and total body clearance were not significantly altered (Table 2).

The p.o. application of OLD after AA did not affect serum concentrations, except for tendencies for higher concentrations in quails, and for the second part of the curves in chickens (Fig. 3 and Fig. 4). Higher values of the F_{abs}% were observed in both species (Table 3). The F_{abs}% in chickens was increased from 21.61% to 37.67%, and the relative one was

Table 3. Pharmacokinetic parameters of oleandomycin in chickens and quails after p.o. administration alone and after ascorbic acid (x ± SEM)

Parameters	Chickens (40 mg/kg)		Japanese quails (40 mg/kg)	
	OLD	OLD + AA	OLD	OLD + AA
C_{max} (μg/ml)	1.41 ± 0.53	1.49 ± 0.37	1.44 ± 0.38	3.996 ± 1.7
t_{max} (h)	1.67 ± 0.4	3.16 ± 0.78	1.7 ± 0.3	1.1 ± 0.37
β (h^{-1})	0.369 ± 0.04	0.371 ± 0.056	0.595 ± 0.098	0.551 ± 0.13
$t_{1/2\beta}$ (h)	2.18 ± 0.25	2.85 ± 0.65	1.37 ± 0.24	1.68 ± 0.46
MRT (h)	4.58 ± 1.02	8.27 ± 1.98	2.77 ± 0.33	2.90 ± 0.69
AUC (μg/ml.h)	3.87 ± 0.31	5.03 ± 0.67*	3.6 ± 0.69	8.79 ± 3.22
AUMC	18.85 ± 4.57	65.34 ± 31.48^{+}	9.43 ± 1.32	18.68 ± 3.29*$^{+}$
Fabs (%)	21.61 ± 2.40	37.67 ± 9.17	23.99 ± 9.0	28.52 ± 6.1

* Statistically significant at P≤0.05 up to Student's *t*-test; $^{+}$ Statistically significant at P≤0.05 up to Mann Whitney U test;
β - terminal (elimination) rate constant; $t_{1/2\beta}$ - terminal elimination half-life; C_{max} - maximum serum levels; t_{max} - time of C_{max}; AUC - area under the concentration-time curves; AUMC - area under the first moment curve; MRT - mean residence time, F_{abs}% - absolute bioavailability

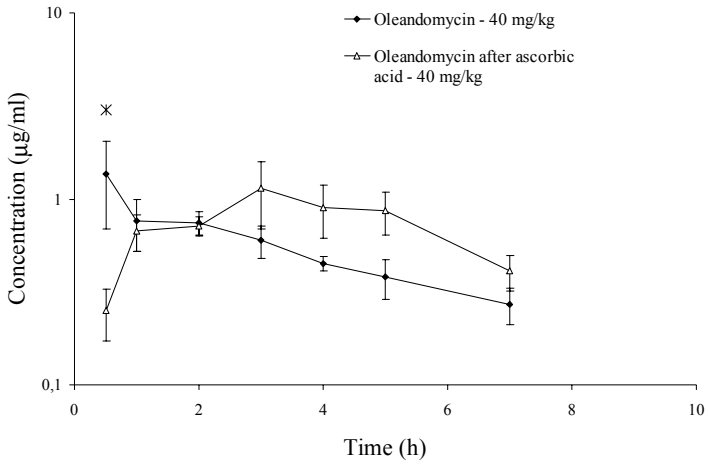

Fig. 4. Serum concentrations (mean ± SEM) of oleandomycin after oral administration alone and after oral administration of ascorbic acid for 7 days at a dose rate of 0.15 mg/l water in chickens (n = 6), Ć Statistically significant at P≤0.05 up to Student's *t*-test

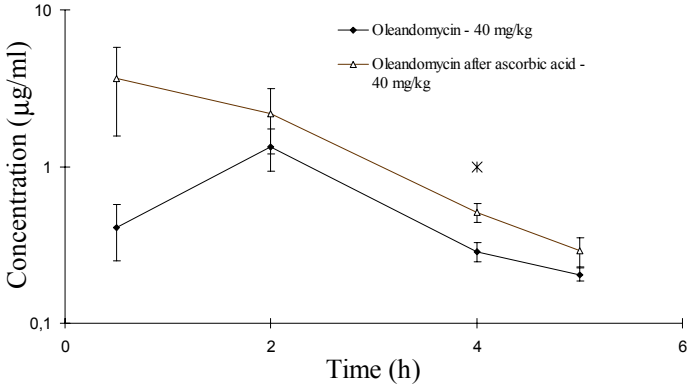

Fig. 5. Serum concentrations (mean ± SEM) of oleandomycin after oral administration alone and after oral administration of ascorbic acid for 7 days at a dose rate of 0.15 mg/l water in Japanese quails (n = 5), Ć Statistically significant at P≤0.05 up to Student's *t*-test

176.8%. In quails F_{abs}% were 23.99% and 28.52%, respectively, with the relative being 239.3%.

Discussion

According to LAKRITZ et al. (1999) microbiologic assays are comparable with high-performance liquid chromatography assays and they may provide adequate information regarding the disposition of macrolide antibiotics.

Our results obtained after a single OLD administration are similar to those reported by other authors for pigeons, ducks (*Anas plathyrhynchos*) and chickens (LASHEV, 1999). The Cl_B values in chickens (79.7 ml/kg/min) and in ducks (57.23 ml/kg/min) are similar to ours, and the values of F_{abs}% after p.o. oleandomycin administration are also close to those reported by LASHEV et al. (1999). At the same time, they reported higher values of $t_{1/2\beta}$ and MRT in comparison with our results. This may be due to different body mass, breed and age of chickens, and species differences between ducks used by us and by other authors (LASHEV et al., 1999). Pharmacokinetic parameters in the present study were also similar to those reported for

mammals (DUTHU, 1985) and show a tendency towards longer OLD elimination half-life in birds than in mammals.

Our results suggest that AA administration through drinking water in chickens, musk ducks and quails for seven days induces changes in the pharmacokinetics of i.v.-applied oleandomycin. AA treatment increases antibiotic concentrations in the serum, but in ducks does not influence rate of distribution. Rate of elimination was diminished and $t_{1/2\beta}$ was prolonged in all bird species used. It was significantly delayed in chickens, but in quails and ducks only tendencies in the same direction were registered. A tendency also existed for prolongation of MRT. Similar changes in AUC and Cl_B were observed in chickens and ducks, but such tendency was not valid for quails. In another investigation, NOVOTNY and MILNER (1993) reported that ascorbic acid increased cellular selenium retention.

OLD administered p.o. after ascorbic acid was associated with prolonged $t_{1/2\beta}$ and higher bioavailability in chickens and in quails.

The i.v. application of OLD in chickens at a dose of 15 mg/kg up to our results provides levels higher than the minimum inhibitory concentrations (MIC; over 0.15 mg/ml) for 4.5 hours. The i.v. application of oleandomycin in musk ducks at a dose of 15 mg/kg provides MIC over 0.15 mg/ml for 5.4 hours. The combination of oleandomycin and ascorbic acid in similar conditions allows a prolongation of the dosage intervals in both species for 6 hours. These intervals were calculated according to the formula $t = (\ln B - \ln 0.15)/\beta$ (BAGGOT, 1977) and the pharmacokinetic parameters calculated by us. Using the same formula it was calculated that after *i.v.* application of OLD in quails the applied dose provides concentrations over 0.15 mmg/ml for 5.2 hours. The combination allows the interval to be prolonged to 5.7 hours.

The use of a single dose of 40 mg/kg p.o. in chickens and quails provides serum OLD levels over 0.15 mg/ml for 7.5 hours and 6 hours, respectively. After AA it is necessary for these doses to be lowered to 68.35 % in chickens and to 45.54% in quails. If the dose of 40 mg/kg is accepted for use, then intervals should be 10 and 7 hours, respectively. These calculations were made using the relationship: $B = C_{min} \times (1 - e^{-\beta\tau}) / e^{-\beta\tau}$, where C_{min} = MIC and τ = dose interval.

In conclusion, the present study suggests that ascorbic acid slightly prolonged OLD elimination in the three birth species studied. There are some species-related differences in drug interactions between ascorbic acid and oleandomycin, but from a pharmacokinetic point of view this combination is admissible.

References

BAGGOT, J. D. (1977): Some Important Principles of Drug Dosage. In: Principles of Drug Disposition in Domestic Animals: The Basis of Veterinary Clinical Pharmacology. W. Saunders Company, Philadelphia, pp. 197-205.

DUTHU, G. S. (1985): Interspecies correlation of the pharmacokinetics of erythromycin, oleandomycin and tylosin. J. Pharm. Sci. 74, 943-946.

HEGEROVA, E., J. SIMUNEK (1988): Influence of coccidiostats on the pharmacokinetics of orally administered sulphonamides. 4th Congress of the EAVPT. Budapest, (Abstracts), p. 66.

LAKRITZ, J., W. D. WILSON, J. M. MIHALYI (1999): Comparison of microbiologic and high-performance liquid chromatography assays to determine plasma concentrations, pharmacokinetics, and bioavailability of erythromycin base in plasma of foals after intravenous or intragastric administration. Am. J. Vet. Res. 60, 414-419.

LASHEV, L. (1998): Pharmacokinetics of apramycin and sulphachlorpyridazine coadministered with flavophospholipol and avoparcin to chickens. Bulg. J. Vet. Med.1, 71-76.

LASHEV, L., D. DIMITROVA, V. LASHEVA (1999): Pharmacokinetics of oleandomycin in birds. Current Trends in the Development of Fundamental and Applied Sciences. Volume 1, Stock breeding, Plant-growing and Veterinary medicine (Bg), pp. 378-381.

MOUTAFCHIEVA, R. (1989): Effects of some nutritive antibiotics on the pharmacokinetics of tylosin in chickens.Vet. sbirka (Bg) 1-3, 19-22.

NOVOTNY, J. A., J. A. MILNER (1993): Impact of ascorbic acid on selenium-induced growth inhibition of canine mammary tumor cells in vitro. J. Nutr. Biochem. 4, 341-345.

PATHANASOPHON, P., T. TANTICHAROENYOS, L. TRONGWONGSA (1990): Outbreaks of antipestifer infection in Thailand. Proceedings of the 7th Congress of the Federation of Asian Veterinary Associations (FAVA). Bangkok, pp. 371-380.

RAMADAN, A., M. S. HANAFY, N. A. AFIFI (1992): Effect of pantotenic acid on disposition kinetics and tissue residues of sulphadimidine in chickens. Res. Vet. Sci. 52, 337-341.

SHARMANOV, T. (1979): Ascorbic acid. In: Experimentally vitaminology. (Ostrovski, U., Ed.), Minsk, Science and Technology, pp. 481-500.

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SAŽETAK

Istra•en je učinak askorbinske kiseline primijenjene u vodi za piće u dozi 15 mg/l u tijeku 7 dana na farmakokinetiku oleandomicina u kokoši, mošusnih pataka i japanskih prepelica. Poluvrijeme eliminacije oleandomicina bilo je duže u ptica tretiranih askorbinskom kiselinom, a bioraspoloživost mu je porasla u kokoši i prepelica nakon peroralne primjene. Opažene su vrsne razlike u raspodjeli oleandomicina. U usporedbi s kokošima i japanskim prepelicama, u mošusnih pataka zabilježene su niže vrijednosti konstanti opsega eliminacije. Volumen raspodjele (V_{ss}) bio je veći u prepelica. Zaključuje se da askorbinska kiselina ne utječe značajno na raspodjelu oleandomicina u tretiranih ptica.

Ključne riječi: oleandomicin, farmakokinetika, askorbinska kiselina, interakcija, ptice