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CHARACTERISTICS OF PHARMACOKINETICS OF ANTIBACTERIAL DRUGS IN BIRDS: A REVIEW

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Summary

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Literature data and reports about the pharmacokinetics of representatives of the most important groups of antibacterial drugs applied in veterinary medicine (sulphonamides, fluoroquinolones, penicillins, aminoglycosides, tetracyclines, macrolides) in various domestic, exotic and wild avian species are reviewed. The principal characteristics of their behaviour in avian organism are summarized. The principles of antibacterial drug pharmacokinetics, related to intra- and inter-species differences, as well as to the route of administration are emphasized.

Key words: antibacterials, birds, pharmacokinetics

INTRODUCTION

The routine clinical veterinary practice often comes across other than the commonly encountered animal species. A considerable part of them are avian species. The body weight of avian representatives, subjects to veterinary care, ranges from several grammes to more than 100 kilogrammes. This fact, apart being fascinating, is associated to clinical problems because of species-related anatomo-physiological differences in the systemic behaviour of xenobiotics. The pharmacokinetic information for most avian species, including domestic ones, is inadequate or lacks. It is continously increasing with time, particularly intensively for the relatively rarely studied species, demanding to summarize the new data and to present them in an user-friendly manner. This would finally reflect upon the result of veterinary activities – the treatment or, more precisely, the determination of dosages of drugs and the intervals between treatments.

Because of the specificity of action of antibacterial drugs, the precise dosage is at first necessitated from the requirement for a continuous effect upon pathogenic agents (for those with bacteriostatic type of antibacterial activity) and subsequently, from the risk of onset of bacterial resistance to chemotherapeutics – a frequent result of inadequate dosage. That is why, the study on species-related differences with regard to mentioned problems is important in order to perform an adequate therapy.

On the basis of previous studies, the species-related variations in drugs behaviour could be summarized as variations in drug absorption, distribution, metabolism and excretion. The differences in drug elimination are relatively the most extensively studied and the most important (a

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particular significance is paid on liver biotransformation). Commonly, those variations are caused by the variable intensity of oxidative, reducing and hydrolytic processes in domestic animals (Vree et al., 1985a, Van't Klooster et al., 1992, Witkamp et al., 1992).

The principal sources for the specificity in absorption and elimination are predetermined by the morphological and functional particularities of various avian species. Avian gut characteristics influence the absorption rate. The pH of its different parts is specific. The blood volume is 6.5–10% of body weight, the plasma volume – 4–8% and albumin concentrations less than 10%. The body temperature is about 40 °C. The mass of lungs is lower than that in mammals and their volume does not changes within a respiratory cycle. In part of birds there is no bile. The liver functions as an excretory organ for xenobiotics and their metabolites. The kidneys are relativey larger compared to mammalian kidneys. There are considerable interspecies morphological variations and physiological particularities. Generally, the glomerular filtration rate in birds is lower that that in mammals for an equal body mass. Avian glomerular filtration is not constant. The option for tubular secretion of drugs is unknown although most waste products are excreted by secretion. The drug reabsorption from tubular filtrate is realized via diffusion, the rate of reabsorption and the amount of reabsorbed substance being dependant on the degree of ionization. Avian kidneys are with a limited concentration capacity with a ratio of urine to blood osmolality of 2:1. Urine pH in female birds varies between 4.7 and 8 depending on the hatching period, while that of males is about 6.4 (Anadón, 1999).

The present report aims to recapitulate the results of numerous studies upon the pharmacokinetics of the most commonly used antibacterial drugs in different avian species with emphasis on absorption, disposition, metabolism and excretion, characterized by the respective pharmacokinetic parameters.

SULPHONAMIDES

Sulphonamides show first or zero order pharmacokinetics including cases with capacity limitation in elimination, depending on the applied dose. The rate and degree of absorption of sulphonamides from the site of administration varies in broad limits depending on their structure. The disposition, especially following intravenous application, is clearly affected from the character of drug. The variations are also in a broad range (Pashov, 1983; Nouws et al., 1985; Vree et al., 1985a, 1985b).

Generally, sulphonamides are eliminated via metabolism and renal excretion (Vree et al., 1985b). The involvement of both types of elimination depends on species-related anatomo-physiological characteristics – enzyme activity, renal structure and function.

The biotransformation of sulphonamides normally occurs through two principal phases – those of metabolic transformations and synthetic reactions, respectively. Biotransformation takes place primarily in the liver, but it is found also in lungs, kidneys etc. The principal processes in sulphonamide metabolsim – acetylation and hydroxylation, are not uniform in the various species – chicken, turkey, pigeon, goat and swine (Vree et al. 1985a; Vree et al., 1985b; van Ginneken et al., 1991; Nouws et al., 1993).

The hydroxylation of sulphonamides is less extensively studied. There are a lot of data mostly for sulphadimidine in mammals. The hydroxylation rate is significantly species-dependent (Nouws et al., 1985; Witkamp et al., 1992; Van't Klooster, 1992).

Acetylation is performed by N-acetylase and acetyl CoA. There are interspecies as well as intra-species, genetically determined differences in the activity of those enzymes, thus dividing individuals to rapid and slow acetylators. The activity of N-acetylase varies among species. Acetylation is a part of the reversible process acetylation-deacetylation, and its equilibrum is species-dependent too. Pigeons, for instance, have equal levels of both acetylation and deacetylation (Vree et al., 1985b).

The binding to glucuronic acid is characteristic mainly for "higher" animals (mammals and birds) and is species-specific. As a rule, in birds it could be insignificant.

The specificity of drug structures could play a significant role, determining the presence of variations in the whole metabolism and as a consequance – in that of sulphonamide kinetics. There are for example considerable variations in the metabolism of sulphadimethoxine, sulphamethomidine, sulphadiazine and sulphapyrine, related to the structure of compounds. Some examples for the significant variability in the pharmacokinetics of sulphonamides, determined by the chemical structure and the species are presented in Table 1.

Pigeons acetylate and hydroxylate sulphonamides (namely, sulphametoxazole, sulphadimidine and sulphadimerazine) to hydroxylated and acetylated products. The levels of acetylation reaches 5-10% and that of hydroxylation – 10-40%. Up to 50% of all administered sulphonamides remain unidentified. It is stated that after the oral application of sulphametoxazole, the hydroxylation of the substance is important. Up to 45% of the balance are lacking. Similar data are reported for sulphadimidine after oral administration, the acetylation being at a higher degree and the biological half-life of sulphadimidine in pigeons – 41 min. Both sulphonamides are excreted with urine and faeces in a considerable extent – up to 50%. Sulphamerazine showed a biological half-life of 10 hours with prevalence of acetylation (Vree et al., 1985b). Following an intravenous administration at a dose of 100 mg/kg, sulphacetamide exhibited a poor distribution and a fast excretion ($t_{1/2}$ = 0.77 h) (Lashev, 1998).

The pharmacokinetics of sulphadimidine following oral administration in chickens and Colchide pheasants is similar and depends on the gender and the level of sexual hormones (Lashev, 1998). Its disposition is uniform and the excretion – relatively delayed – $t_{1/2}$ varies between 8.5-9 h in hens and 5.5-6.5 h in Colchide pheasants. Up to 20% of the dose is rapidly acetylated and the rest is hydroxylated, with hydroxylated metabolites being excreted faster. The level of deacetylation is high and comparable to that in pigeons. The concentrations of sulphadimidine and its metabolites in faecal masses are also high. In the eggs of treated birds, the observed levels of sulphadimjdine are relatively high (for a week after the treatment) as well as the levels of its metabolites. The concentrations in white of egg are considerable higher compared to yolk ones (Geertsma et al., 1987). Similar data are reported for sulphamethoxazole and sulphadimethoxine (Vree et al., 1985b).

Table 1. Selected pharmacokinetic parameters of sulphonamides in birds

Sulphonamide	Species	Route of adminis-tration	Dosage (mg/kg)	Parameters						Reference
				$t_{1/2\beta}$ (h)	Vdarea (l/kg)	Cl_B (l/kg/h)	Tmax (h)	Cmax (μg/ml)	F (%)	
Sulphadimidine	Chicken	i.v.	50	8.06	1.16	0.115				Lashev, 1998
		p.o.	50				1.86-2.06	62.07		
	Quails	i.v.	50	1.6	1.29	0.62				Lashev & Mihailov, 1995
	Pheasants	i.v.	50	5.97	0.77	0.092				
	Turkeys	p.o.	50				0.21	58.55		Lashev, 1998
Sulphachlor-pyrazine	Chicken	i.v.	50	4.31–9.11	0.35–0.55	0.03–0.078				Lashev, 1998
		p.o.	50				3.5–6.3	60.4–81.0	45–97	
	Turkeys	p.o.	50				4.32	75.50		
Sulphacetamide	Chicken	i.v.	100	1.38	0.68	0.34				Lashev, 1998
	Pigeons	i.v.	100	0.77	0.34	0.37				
	Pheasants	i.v.	100	1.59	0.52	0.23				
Sulphachlor-pyridazine	Chicken	i.v.	50	3.46	1.09	0.258				Lashev, 1998
	Chicken*	i.v.	50	0.835	0.699	0.594				Lashev, 1998
		p.o.	50	2.67–3.45			1.41	33.10	38.4	
	Turkeys*	p.o.	50	1.80			1.29	18.60		

* 18-days-old birds; $t_{1/2\beta}$ = biological half-life; Vdarea = apparent volume of distribution; Cl_B = total body clearance ; Cmax = maximum serum concentrations ; Tmax = time for Cmax; F(%)= bioavailability.

The disposition and elimination of sulphacetamide in chickens, Colchide pheasants and pigeons are similar (Table 1).

A high degree of absorption following oral application and delayed elimination is observed in chickens, treated with sulphachlorpyrazine and sulphaquinoxaline, both healthy and coccidiotic (El Sayed et al., 1995; Lashev, 1998). The disposition of sulphaquinoxaline is rather uniform in treated birds (El Sayed et al., 1995; Williams et al., 1995). Sulphachlorpyridazine and sulphathiazole are absorbed relatively quickly and incompletely and their excretion is rapid. The biological half-life of sulphathiazole and sulphachlorpyrazine is 1.0-1.4 h and 3.45 h, respectively (Lashev, 1998). The combined oral application of sulphadimidine and trimethoprim in chickens does not show a clear age-related difference in the absorption and the elimination of both substances (Pashov & Mutafchieva, 1992).

In domestic goose, there are no data for the pharmacokinetics of sulphonamides following intravenous application, but both absorption and elimination rates are different after an oral administration. Sulphachlorpyrazine is excreted comparatively rapidly with a biological half-life of 1.89 h while sulphaquinoxaline exhibited a significantly longer half-life – 11 h. Sulphamethoxazole is also excreted relatively slowly (biological half-life of 7 h). The data observed in goose showed a certain delayed elimination of used sulphonamides compared to smaller species, but a high degree of absorption as well (Romvary and Horvay, 1976).

There are no data in turkeys after parenteral application of sulphonamides, but the oral administration of sulphachlorpyrazine, sulphachlorpyridazine and sulphadimidine in turkeys showed a high degree of absorption, concentrations, similar to those in chickens treated with the same doses as well as a comparable elimination rate (Lashev, 1998).

TRIMETHOPRIM AND ITS ANALOGUES

Trimethoprim, as a pyrimidine derivative with an antibacterial and antiprotozoic activity, is applied in combination with various sulphonamides. Formulations intended for oral application are often used for treatment and prophylaxis in birds. After an intravenous application, it shows a first order pharmacokinetics. The one-compartment and two-compartment models and a high volume of distribution are typical (Pashov and Mutafchieva, 1992; Lashev and Mihailov, 1995). Administered orally, trimethoprim exhibited a comparatively high degree of absorption from the gut of chickens – 80-85% (Dagorn et al., 1991; Pashov and Mutafchieva, 1992) and Japanese quails – 41.1% (Lashev, 1998). Its disposition in tissues is uniform (Pashov, 1983) and it is excreted partially unchanged via the kidneys (Löscher et al., 1990). It undergoes a partial metabolism in the liver as well. The biological half-life of trimethoprim in chickens varies between 3.19 h and 5.17 h (Pashov, 1983). In goose, the biological half-life is 2.68 h (Romvary and Horvay, 1976). The values in Japanese quials are lower – 2.27 h (Lashev, 1998). It could be stated, that contrary to mammals, the pharmacokinetics of trimethoprim in birds does not vary significantly. The information about trimethoprim analogues (ormethoprim, adithoprim, baquiloprim or methioprim) is considerably less (Engeli et al., 1993).

PENICILLINS AND CEPHALOSPORINS

The group of penicillins includes substances with significant variances in the chemical structure, chemical and pharmacokinetical behaviour. Their pharmacokinetics following intravenous application is of first order (Bush et al., 1979; Moutafchieva, 1992a, Soenens et al., 1998). The disposition is quite rapid with one-compartment or two-compartment models of disposition and elimination in smaller avian species and a two-compartment model in bigger ones (Dorrestein et al., 1984, 1987, Carseles et al., 1994, Lashev, 1998). They penetrate the interstitial fluid and the lymph (Mattie and Meenhors, 1979, Wise er al., 1980). The tissue penetrating capability is negatively correlated to the percentage of binding to proteins. For aminopenicillins, principal subjects of the present review, this percentage is about 20% (Wise et al., 1980). The elimination is mainly via renal tubular excretion, without data for any capacity limitation. There are practically no metabolites in the blood of treated animals. Therefore, the differences in the pharmacokinetics of penicillins (including species-dependent ones) and particularly in their elimination, are primarily due to species-related variations in the renal function and gut anatomy, when the medication is administered via the oral route.

In birds, aminopenicillins (ampicillin and amoxycillin) as well as phenoxymethylpenicillin are the most commonly used and the most familiar because of the sufficient degree of absorption following oral administration and their antibacterial spectrum. It is believed that the absorption of penicillins from avian gut is incomplete compared to that in mammals and that it is similar for various avian species (Dorrestein et al., 1984; Lashev, 1998) (Table 2).

Ampicillin and amoxycillin have evidenced a significant absorption in pigeons, musk ducks and chickens. The absorption of the latter is almost twice higher ensuring almost double blood concentrations. As to their systemic disposition, both antibiotics showed similar behaviour in pigeons and chickens (Lashev, 1986, Moutafchieva, 1992a, Lashev, 2000) manifested by a good tissue disposition with highest levels in kidneys, liver and lungs (Lashev, 1986). The elimination of both antibiotics is similar. After intramuscular application, the pharmacokinetics of ampicillin and amoxycillin is similar with a high degree of absorption from the site of injection (Dorrestein et al., 1987, Lashev, 1987). Phenoxymethylpenicillin is rapidly absorbed from the gut in chickens, but in a lesser extent than amoxycillin and ampicillin and is excreted faster compared to those two drugs. The disposition of phenoxymethylpenicillin in the tissues of chickens following a single oral application is equal to that observed in pigeons, treated orally with amoxycillin (Lashev, 1987; 2000). The data reported by Chaleva (1978) in chickens treated orally with ampicillin are similar. The highest tissue ampicillin levels are found in kidneys and liver whereas levels in other tissues (muscles, lungs, heart muscle) are usually close to, but lower than serum concentrations. The biliary levels of amoxycillin and ampicillin are high. There is age-related dependence of phenoxymethylpenicillin elimination rate in chickens – it is enhanced in adult birds, the biological half-life being respectively lower compared to that in newly hatched birds (Lashev, 2000). Oxacillin showed an extremely rapid elimination following intravenous adminsitration in chickens. Its

Table 2. Selected pharmacokinetic parameters of penicillins in birds

Antibiotic	Species	Route of adminis-tration	Dosage (mg/kg)	Parameters						Reference
				$t_{1/2\beta}$ (h)	Vdarea (l/kg)	Cl_B (l/kg/h)	Tmax (h)	Cmax (μg/ml)	F (%)	
Amoxycillin	Pigeons	i.v.	100	1.22	151	1.40				Dorrestain et al., 1987
		i.v.	30	0.54	0.5	0.41				Lashev, 1986
		i.m.	100				1.50		57	Dorrestain et al., 1987
		p.o.	117				0.71–1.26		35	
	Chicken	i.v.	10–30	0.58–1.03	0.73–1.00	0.49-1.19				Lashev, 1986
		p.o.	30						35.6	
	Turkeys	i.v.	10–30	0.89–1.12	0.67–1.76	0.4-1.38				Lashev, 1986
		p.o.	30						56.9	
Ampicillin	Pigeons	i.v.	20–100	0.31–0.65	0.95–0.97	1.04-2.14				Dorrestain et al., 1987
		p.o.	100				1.04	8.46	20	
	Chicken	i.v.	20–30	0.56	1.16					Lashev, 1998
Carbenicillin	Chicken	i.v.	30	0.55	1.22	1.63				Unpublished
Oxacillin	Chicken	i.v.	30	0.14	2.40	1.26				Unpublished

* 18-days-old birds; $t_{1/2\beta}$ = biological half-life; Vdarea = apparent volume of distribution; Cl_B = total body clearance ; Cmax = maximum serum concentrations ; Tmax = time for Cmax; F (%)= bioavailability.

persistence in blood in detectable concentrations (0.2 μg/kg) after a dose of 30 mg/kg is within an hour, thus making it inappropriate for use in this species (Lashev, unpublished data) (Table 2). The data obtained after intravenous or intramuscular adminsitration of cloxacillin and flucloxacillin (Dimitrova et al., 1997; Dimitrova, 1999) are similar.

Following oral application, penicillin and especially aminopenicillins showed lower peak concentrations in birds compared to mammals (Lashev, 1987). This fact could be hardly explained by metabolic differences, because such are not known.

Cephalosporins are considerably less studied and used. In Japanese quails, pigeons, ducks, cranes and emus, the pharmacokinetics of intramuscularly applied cephalotin and orally applied cephalexin was similar to that of aminopenicillins. Their biological half-life was between 0.3 and 0.9 h in various species (Bush et al., 1981). There was a correlation between the biological half-life and body weight, the lighter species showing a shorter persistence of the antibiotics in blood.

Known cephalosporins, likewise penicillins, are excreted faster in birds than in mammals (Dorrestein et al., 1984; Lashev, 1998).

TETRACYCLINES

Following intravenous application, tetracyclines remain for a long time in the organism of birds and mammals. They generally follow a two-compartment model of disposition and elimination, but cases of three-compartment model are also described. Their absorption from the gut varies for tetracycline and oxytetracycline depending on their binding to bivalent cations. The results of different studies evidence that some tetracyclines (tetracycline and oxytetracycline) are metabolized in various species, but it is of no significance for their elimination. Following parenteral application, almost 50% or more of systemic oxytetracycline, tetracycline and doxycycline amounts are excreted with urine. The principal mechanisms of elimination is glomerular filtration, but the tubular reabsorption is also possible (Aronson, 1980; Teare et al., 1985). A biliary excretion via an active transport is reported (Aronson, 1980), the biliary concentrations being high because of the small quantity of bile. It is also considered that a considerable part of tetracyclines are excreted through gut mucosa under the form of conjugates or stable complexes that do not influence intestinal microflora. With this respect, the lowest influence is that of doxyxycline (Aronson, 1980). The urinary excretion of intravenously applied oxytetracycline between post treatment hours 2 and 8 was 37.6%, and biliary one – 2.15% (Dyer, 1989). The author states that after an hour, the ratio between biliary and serum concentrations was from 41.4 to 60.8. The biological half-life in turkeys was 0.73 h.

The pharmacokinetics of oxytetracycline is not dose-dependent (Dorrestein et al., 1991; Greth et al., 1993). Intramuscularly administered oxytetracycline at dose rates of 16-22 mg/kg ensures therepeutical levels for 12-24 h in pheasants, owls and parrots (Teare et al., 1985). In turkeys, orally administered oxytetracycline in fasting birds provided up to three-fold higher blood concentrations compared to fed birds.

The absorption of doxycycline from avian gut is the highest compared to that of other tetracyclines and varies between 25 and 83.7% vs 3.3-10% for others, respectively (Martinez-Larranaga et al., 1985). Doxycycline metabolites are not

found out (Santos et al., 1996). Its disposition is uniform in kidneys, liver, lungs and muscles in chickens. It persists for a long time – up to 5 days following a single administration (Anadón et al., 1994). Following intravenous and oral application in turkeys, age-dependent differences in the pharmacokinetics are observed (Santos et al., 1996). The absorption rate depends also on the nutrition. A considerable higher bioavailability was observed in fasting turkeys compared to those, fed prior to the treatment (Santos et al., 1996). The same relationship, although in a lesser extent, is reported in chickens (Laczay et al., 2001). Doxycycline persisted for a long time in the blood of vultures following intramuscular and subcutaneous application with biological half-life within 58.9–85.9 h (Greth et al., 1993). In domestic pigeons, the antibiotic provided therapeutical concentrations for 148 h after a single injection of 75 mg/kg (Dorrestein et al., 1981).

A faster elimination of doxycycline was observed in doves compared to pigeons, explained by the lower body weight and the higher level of basic metabolism (Dorrestein et al., 1990). The authors suggest that inter-species differences in the pharmacokinetics of tetracycline antibiotics are determined by variances in their renal, biliary and gastrointestinal excretion, by the various degree of binding to blood and tissue proteins as well as by their disposition. Most probably, rolytetracycline is the only drug, where those differences are significantly dependent to metabolism. Those features of tetracyclines determine their wide and continuous application in birds.

AMINOGLYCOSIDES

The pharmacokinetics of aminoglycoside antibiotics in both mammals and birds is usually studied following parenteral application because of their poor absorption in the gut. After intravenous administration, they show a first order pharmacokinetics and most commonly, a two-compartment model of disposition and elimination, as evidenced by the profile of serum concentration curves. They are poorly bound to serum proteins except for streptomycin and their disposition is limited to within the extracellular fluid (Baggot et al., 1981, Kösters et al., 1984; Brown and Riviere, 1991). Thus, all aminoglycosides have a low volume of distribution and lower tissue concentrations compared to serum ones. The elimination occurs by glomerular filtration. An accumulation and prolonged persistence in the renal cortex are observed (Baggot et al., 1981). Considering that the glomerular filtration in birds is twice lower compared to that in mammals and that the pharmacokinetics of gentamicin is comparable to that in mammals following intravenous adminsitration, it could be presumed that tubular reabsorption in birds is of little significane (Dorrestein et al., 1984).

There are numerous reports from comparative studies in birds, treated with aminoglycosides, with gentamicin and amikacin being most widely studied especially in exotic birds (Table 3).

The intramuscular and intravenous adminsitration of gentamicin at doses of 5–10 mg/kg in various avian species (parrots, chickens, hawks, owls, eagles, turkeys) is not related to significant pharmacokinetic differences. An one-compartment or two-compartment models of disposition and elimination depending on the route of application are determined. The biological half-life is from 0.5 to 2.46 h, being longer in heavier species. The bioavailability following intramuscular application is almost 100% (Bird et al., 1983;

Table 3. Selected pharmacokinetic parameters of aminoglycosides in birds

Antibiotic	Species	Route of administration	Dosage (mg/kg)	Parameters						Reference
				$t_{1/2\beta}$ (h)	Vdarea (l/kg)	Cl_B (l/kg/h)	Tmax (h)	Cmax (µg/ml)	F (%)	
Gentamicin	Parrots	i.m.	5	0.53-1.18						
	Chicken	i.v.	5	3.38	0.23	0.46				Pedersoli et al., 1990
		i.m.	5				0.62	20.7	95	
	Hawks	i.v.	10	1.35	0.24	0.125				Bird et al., 1983
	Owls	i.v.	10	1.93	0.23	0.085				
	Eagles	i.v.	10	2.46	0.21	0.061				
	Turkeys	i.v.	5	2.57	0.19	0.050				Pedersoli et al., 1990
		p.o.	5				0.81	28.82	102	
Amikacin	Parrots	i.v.	10	0.90	0.18	0.142				Gronwell et al., 1989
		i.m.	15	1.29					106	
	Chicken	i.v.	10	1.44	0.23	0.109				El Gamal et al., 1992
		i.m.	20						91	
Apramycin	Chicken	i.v.	10	1.67	0.078	0.182				Lashev, 1998

$t_{1/2\beta}$ = biological half-life; Vdarea = apparent volume of distribution; Cl_B = total body clearance ; Cmax = maximum serum concentrations ; Tmax = time for Cmax; F (%)= bioavailability.

Table 4. Selected pharmacokinetic parameters of oleandomycin in birds

Species	Route of administration	Dosage (mg/kg)	Parameters						Reference
			$t_{1/2\beta}$ (h)	Vdarea (l/kg)	Cl_B (l/kg/h)	Tmax (h)	Cmax (µg/ml)	F (%)	
Pigeons	i.v.	10	2.38	15.3	86.0				Lashev, 1986
	p.o.	20						57.0	
Chicken	i.v.	10	1.35-2.66	4.44-9.98	54.18-79.7				Lashev, 1986
	p.o.	20-40				1.67	1.41	21.60-46.23	
Ducks	i.v.	15	3.47	17.26	57.23				Lashev, 1986
	p.o.	20						37.70	
Musc ducks	i.v.	15	1.76-1.91	6.78	57.35				Haritova, 2001
Japanese quails	i.v.	30	1.25	3.30	50.28				
	p.o.	40				1.7	1.44	23.99	

$t_{1/2\beta}$ = biological half-life; Vdarea = apparent volume of distribution; Cl_B = total body clearance ; Cmax = maximum serum concentrations ; Tmax = time for Cmax; F (%) = bioavailability.

Pedersoli et al., 1989; Itoh, 1993). The pharmacokinetics of amikacin after intravenous and intramuscular adminsitration to parrots and chickens is similar to that of gentamicin (Gronwall et al., 1989; Pedersoli et al. 1990; El-Gammal et al., 1992; Ramsay and Vulliet, 1993).

Tobramycin is characterized with a short stay in pigeons following intravenous and intramuscular application with biological half-life from 0.82 to 1.44 h and lower bioavailability following intramuscular application – 54%. The disposition of this antibiotic is the same as in other aminoglycosides (Dimirova et al., 1998).

When the intramuscular adminstration of aminoglycosides is indicated, their high nephrotoxicity, especially in diseased birds with a limited glomerular filtration, have to be considered.

MACROLIDES

Data about macrolides are relatively few with the exception of tylosin. This group is characterized by a high degree of distribution and high tissue concentrations. Inter-species differences are reported for tylosin (Locke et al., 1982), that is the most commonly used. Following an intramuscular application of tylosin in quails, pigeons, cranes and emus, it is observed that smaller birds have a significant shorter elimination half-life and that the peak concentrations were higher. According to the authors, there is a positive correlation between body mass and the elimination half-life of tylosin. The relatively delayed metabolism in big emus are the cause for the longer period of elimination. The bioavailability following oral application in chickens is 23.5% and the biological half-life after intravenous application – 0.99 h. The relationship between body weight and the elimination half-life reflects upon the dosage of tylosin in various avian species. As a rule, the dose of 20 mg/kg applied intramuscularly, ensures therapeutical concentrations for 24 h. The usual dose for oral adminsitration is 100 mg/kg.

The intravenously administered oleandomycin at doses between 10 and 30 mg/kg showed a rapid distribution rate in pigeons, chickens, musk ducks and Japanese quails. The biological half-life ranges from 1.25 h (Japanese quail) to 4.85 h (musk ducks). The bioavailability following intravenous administration is 22-57% (Lashev et al., 1999) (Table 4).

The oral application of 50 mg/kg erythromycin as well as the subcutaneous injection of 10 mg/kg in chickens showed a persistence not longer than 6 h because of the rapid elimination. The biological half-life is 0.67 h and the bioavailability - 3.17% and 14% following oral and subcutaneous administration respectively (Moutafchieva, 1988; 1992b).

The semi-synthetic macrolide antibiotic tilmicosin is interesting, but the data abour its pharmacokinetics are very insufficient. Its intracellular penetration is responsible for its prolonged elimination (Shryock and Scorneaux, 1997).

It could be stated that the data from comparative studies upon macrolides are limited, but allow to make conclusions with regard to the variability of gut absorption, the high tissue distribution rate and high tissue concentrations in treated birds and the rapid elimination rate, that is allometrically dependent on body weight similarly to other drugs.

FLUOROQUINOLONES

Fluoroquinolones are a relatively new groups of synthetic substances with a strong antibacterial activity performed by minor concentrations against a broad

spectrum of microorganisms, including those, resistant to the majority of other antimicrobial agents. They resemble in both structure and mechanism of action to nalidixic and oxolinic acids – the first applied representatives of this group (Brown, 1996). Considering that fluroquinolones are a relatively new group of antibacterial compounds the studies referring to them are mainly from the last decade and despite the intensive research, the data for their application in veterinary medicine are still incomplete. The publications are from studies upon the commonest quinolones, used in birds: enrofloxacin (Dorrestein and Verburg, 1988; Chen et al., 1994; Anadón et al., 1995; Bailey et al., 1997; Garcia et al., 1999; Waxmann, 2000), ciprofloxacin (Garcia et al., 1999, Ata and Sharif, 1997), pefloxacin (Moutafchieva, 1997), sarafloxacin, enoxacin, danofloxacin (Knoll et al., 1999), ofloxacin (Liu and Fung, 1997), difloxacin (Van Den Hoven, 2000), fleroxacin (Martinez-Larranaga et al., 2000), marbofloxacin (Martinez-Larranaga et al., 1997; Diaz et al., 2000), norfloxacin (Anadón et al., 1992). The dosages are between 2 and 10 mg/kg. Aside from domestic birds (chicken, turkey, pigeon), the pharmacokinetics of fluroquinolones is studied in ostriches, hawks, owls, vultures (Table 5). The preferred dose for oral application is 5-10 mg/kg. The pharmacokinetic behaviour of the various representatives is similar, differing mainly in the elimination rates. After an intravenous administration they display a two-compartment model of distribution and elimination. Their tissue disposition is uniform. The biological half-lifes of all studied compounds varies from 1 h (ostriches) to 7 h (vultures), the commonest values being 3-6 h. The volume of disribution (Vd_{area}) is most frequently close to 1 l/kg but values of 2 l/kg and higher are also reported (Chen et al., 1994). The absorption of fluroquinolones from the gut is different. The bioavailability in chickens varies from 57% (norfloxacin) to 100% (ofloxacin) (Liu and Fung, 1997). The achievement of peak concentrations following both intramuscular and oral application comes about relatively rapidly – between 42 min for norfloxacin in turkeys and ciporfloxacin in chickens and 3.5 h for enrofloxacin in chickens. No significant inter-species variance in absorption rate and degree (the latter being 100%) is reported (Lavy et al., 1994; Knoll et al., 1999). In the organism, fluoroquinolones undergo a partial metabolism via oxidation and binding to glucuronic acid (Anadon et al., 1992). The elimination occurs mainly via glomerular filtration (Wolfson abnd Hooper, 1991). After the application of cited doses, fluroquinolones ensure therapeutical concentrations for more than 24 h depending on the sensitivity of microbial agents.

The variances in the pharmacokinetics of antibacterial drugs in the representative of the *Aves* class could be anticipated in connection with the evolutionary determined interspecies biological differences and especially those among the higher rank taxonomic entities – genera, families, divisions etc. The species-related features, generated within the course of evolution, based on individual genotypic differences and those among the genofunds of the various populations, determine to a great extent the reaction of living organisms towards definite pharmacological substances and namely, the variability in the degree of response and in pharmacokinetic parameters.

Table 5. Selected pharmacokinetic parameters of fluoroquinolones in birds

Quinolone	Species	Route of administration	Dosage (mg/kg)	Parameters						Reference
				$t_{1/2\beta}$ (h)	Vdarea (l/kg)	Cl_B (l/kg/h)	Tmax (h)	Cmax (µg/ml)	F (%)	
Enrofloxacin	Chicken	i.v.	5–10	5.57–10.29	1.77–4.31	2.48–10.5				Knoll et al., 1999
		p.o.	5–10				1.5–1.64	1.88–2.44	57–89	
	Pigeons	i.v.	5–10	3.32–3.67	1.37–1.47	0.27				Dorrestein et al., 1988
		p.o.	5–10				2.51–2.86	2.01–3.62	87–92	
	Ostriches	i.v.	5	1.0	5.5					Waxman et al., 2000
	Vultures	i.v.	5	6.55–7.13						Bailey et al., 1997
Norfloxacin	Chicken	i.v.	8	7.99	3.14	0.36				Anadón et al., 1992
		p.o.	8				0.3	1.95	57	
	Turkeys	i.v.	10	1.6	6.89	0.56				Gilkarov & Ziv, 1994
		p.o.	40				0.75	0.88	39.9	
Marbofloxacin	Chicken	i.v.	2	5.26	1.33	0.17				Martinez-Laranaga et al., 1997
		p.o.	2					5.79	129	
Danofloxacin	Chicken	i.v.	5	6.62–6.73	10.2	1.41				Knoll et al., 1999
		p.o.	5				1.5	0.47	99.2	
Pefloxacin	Chicken	i.v.	10	3.33	2.28	0.475				Moutafchieva, 1997
		p.o.	10	6.68			0.66	1.84	73.4	
Difloxacin	Chicken	i.v.	5	2.30	2.91	0.878				Van den Hoven, 2000
	Turkeys	i.v.	5	2.20	5.19	1.687				

$t_{1/2\beta}$ = biological half-life; Vdarea = apparent volume of distribution; Cl_B = total body clearance ; Cmax = maximum serum concentrations ; Tmax = time for Cmax; F(%)= bioavailability.

At the same time, it is known that the variability of pharmacokinetic parameters among individuals could be due to factors, different from those, that are determined by the genotype, such as the physiologuical condition, the functional status of nervous system, the actual immune status, the housing and feeding of birds etc. The answer to the question about the genotype-determined differences in the behaviour of drugs could partly be obtained by studies upon inbred anmimals. In this case, the interpretation of results has to be done from two points of view. The first is related to the use of inbred animals, where the high degree of homozygosity, resulting from the inbreeding, guarantees greatly the similarity in the respoonse of individuals to the studied drug. The high degree of homozygosity in inbred animals would give a result that could be accepted as true only for the respective inbred population. Therefore, the interpretation of the results from the treatment could not be valid for the species in general. The second aspect of the species-specific response of experimental biological subjects to drugs is related to the fact that such pharmacological studies have to be performed on groups of non-inbred animals, representative of a given species, that are as larger as possible. Thus, the individual responses of heterogenic genotypes would be detected and this would result in a bigger variability in the data from the study and consequently, would guarantee the formation of a clearer and more confident idea for the response of the species as a whole as well as for the inter-species differences in the pharmacokinetics of studied drugs.

The comparison of results from numerous pharmacokinetic studies upon antibacterial drugs, antibiotics, sulphonamides, fluoroquinolones and pyrimidine derivatives in various avian species indicates a similar pharmacokinetics of drugs with a comparable chemical structure. The inter-species differences are significantly less than those, shown in mammals. They could be due to the specific chemical structure that determines the systemic response after the administration of the substance and at a higher extent, to species-related particularities. A further role could be attributed to the significance of the different body weight in various species for the intensity of metabolism (Kirkwood, 1983a; 1983b, Kirkwood and Widdowsson, 1990; Kirkwood and Merriam, 1990).

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