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Original Contribution

PHARMACOKINETICS OF TOBRAMYCIN IN BROILER CHICKENS

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ABSTRACT

The pharmacokinetics of tobramycin was investigated in 6 weeks old broiler chickens after three ways of administration (i.v., i.m. and p.o. at doses of 5 mg/kg, for each route and 20 mg/kg orally). Microbiological method was used for the antibiotic determination and non-compartment analysis for pharmacokinetic calculations. It was observed that tobramycin was absorbed very well after i.m. and poorly after oral administration. Its distribution was relatively high compared to other aminoglycosides and other species and was eliminated quickly.

Key words: tobramycin, pharmacokinetics, chickens

INTRODUCTION

Tobramycin is relatively new and still not widely used in the veterinary practice broad spectrum aminoglycoside antibiotic. Information about the pharmacokinetics of the other aminoglycoside antibiotics exists for birds but in this direction tobramycin is still scarce. Only one paper treating its pharmacokinetics in pigeons is available. The respective papers for mammals are more and are related to goats, cats, rabbits and horses (1, 2, 3, 4, 6).

Having in mind the possibility for use of this antibiotic in treating birds it is reasonable to study its pharmacokinetics in the relevant species as prelude to providing information on adequate doses. This study is especially important for members of the aminoglycoside group, which are toxic.

Therefore the aim of the present paper was to study the pharmacokinetics of tobramycin in chickens after its intravenous, intramuscular and oral administrations.

MATERIALS AND METHODS

Tobramycin sulfate (activity 690 IU provided by Balkanfarma Ltd, Sofia, Bulgaria) was used as a 5% (w/v) aqueous solution. The sterile solution was prepared prior to its administration. The doses (mg/kg BW) according to the drug activity in IU/mg and the injection volume were calculated for each bird.

Twenty-four healthy chickens, 6 weeks old, weighing from 440 to 485 g, were used. The birds were allowed a 7-day adaptation period prior to the study. They were housed (in room temperature 20°C), according to the requirements of the species. Food (without antibiotics and coccidiostats) and water were supplied *ad libitum*.

All birds were divided into 4 groups of 6 animals and treated with a single dose of tobramycin as follows:

- I group with 5 mg/kg BW intravenously (*i.v.*);
- II group with 5 mg/kg BW intramuscular (*i.m.*);
- III group with 5 mg/kg BW orally;
- IV group with 20 mg/kg BW orally.

All treatments commenced between 8.00 and 8.30 h. The intravenous administration was in the brachial vein and intramuscular injection – in the pectoral muscles. The oral introduction was intraingluvially.

Prior to and after the intravenous treatment at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hour blood samples from the brachial vein (not treated one was used) were collected from all birds included. Blood samples after *i.m.* and oral administrations were collected in the same time intervals excluding the fist one.

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The volume of the blood samples was 0.5 ml. The blood samples were stored at room temperature for 2 h. Serum was collected after centrifugation at 1800 g for 20 min. Serum was stored at – -20°C prior to analyses. Antibiotic assay was performed after 4 days.

The serum tobramycin concentrations were determined by a microbiological method using *Bacillus subtilis* ATCC 6633 as a test microorganism. The standard solutions were prepared in serum collected from untreated chickens of the same age. The limit of quantification was 0.04 μg/ml, the limit of detection – 0.03 μg/ml. The linearity presented as r^2 was 0.9898. The intra-assay and the inter-assay coefficients of variations were 9.90 and 13.3 respectively.

Pharmacokinetic calculations were performed using compartmental analysis by computer program Winnonlin 4.01.

RESULTS AND DISCUSSION

Serum tobramycin concentrations (presented on **Table 1**) showed that the antibiotic was detectable in the blood of the treated birds very soon after treatment, but their values measured depended on the method of treatment. These results are comparable to the same reported by other authors used different species (1, 2, 3, 4, 6).

Table 1: *Blood serum concentrations of tobramycin in chickens treated by different ways and doses*

Time after treatment (h)	***Way and doses of treatment***		
	Intravenous 5 mg/kg	***Intramuscular 5 mg/kg***	***Oral 20 mg/kg***
0,083	11,64±1,79	NI	NI
0,25	5,80±0,87	5,10±1,15	<0,04
0,5	4,30±0,67	5,47±0,23	0,04±0,02
1	2,31±0,40	6,00±0,45	0,08±0,02
2	1,80±0,21	3,60±0,16	0,09±0,03
3	1,35±0,18	2,40±0,24	0,08±0,02
4	0,53±0,06	2,40±0,05	0,05±0,01
6	0,24±0,02	0,57±0,03	<0,04
8	0,18±0,01	0,32±0,04	<0,04
24	<0,04	<0,04	NI

NI – Not investigated

The values of the calculated pharmacokinetic parameters are presented on **Table 2**. We can make the following suggestions: Tobramycin has pharmacokinetics typical for aminoglycoside antibiotics in chickens. It means low degree of distribution and relatively fast elimination. Compared to other species the extent of distribution was higher (Vss=0.781 l/kg) compared to the data found in pigeons (the only bird species for which data are available) the elimination in chickens was slower. The values of t1/2 (0.82 h) in this species were two-fold lower compared to chickens (**Table 2**).

Table 2: *Pharmacokinetic parameters of tobramycin in chickens after different ways of treatment*

Parameters (units)	***Way and doses of treatment***		
	Intravenous 5 mg/kg	***Intramuscular 5 mg/kg***	***Oral 20 mg/kg***
C^o (μg/ml)	14,95±3,48		
βh^{-1})	0,3589±0,0597	0,4661±0,0377	0,4303±0,0355
$t_{1/2}$ (h)	1,84±0,30	1,60±0,12	1,67±0,15
AUC (μg/ml.h)	12,65±0,53	19,65±0,40	0,393±0,102
Vda (ml/kg)	1041,8±111,4		
Cl_B ml/h/kg	401,5±16,97		
AUMC (μg/ml.h^2)	24,29±21,19	51,56±1,68	1,317±0,310
MRT (h)	1,93±0,10	2,63±0,09	3,41±0,19
V_{ss} (ml.kg)	768,4±35,53		
T_{max} (h)		0,71±0,14	1,83±0,31
C_{max} (μg/ml)		7,12±0,80	0,106±00,28
MAT (h)		0,69±0,15	

The muscular injection was followed by fast and complete absorption. The value of the bioavailability was higher than 100% but in pigeons its value was only 53.7% (1). The rate of elimination after *i.m*. administration was practically equal in both bird species. After oral administration to chickens tobramycin is absorbed in very low extent from the digestive tract. The dose of 5 mg/kg did not provide any detectable blood levels. After dose of 20 mg/kg the antibiotic was detected in the blood in very low levels. The bioavailability after this way of dosing was 0.53%. It means the absorption is much lower than the calculated for gentamicin and apramycin in chickens given the same doses by the same mode of administration (5). Our data for the pharmacokinetics of tobramycin in chickens are close to those found in pigeons, rabbits and dogs treated by the same methods (2, 3, 4, 6); these data include the volume of distribution which is comparatively higher in chickens.

CONCLUSIONS

On the bases of our data we could conclude that any systemic effect of tobramycin is expected after parenteral (intravenous or intramuscular) injection. After oral administration its antimicrobial effect is limited to the digestive tract.

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