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Original Article

PHARMACOKINETICS OF ZINC IN BROILER CHICKENS AFTER SINGLE INTRAINGLUVIAL ADMINISTRATION WITH ZINC ASPARTATE

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Summary

The pharmacokinetics of zinc was investigated in broiler chickens after single crop intubation of 50 mg/kg 5% zinc aspartate suspension in 2% carboxymethyl cellulose solution. Blood serum zinc concentrations were assayed on a biochemical analyzer. The pharmacokinetics of zinc was evaluated using two approaches – compartmental method and non-compartmental analysis using pharmacokinetic software (TopFit, v. 2.0). After the intraingluvial application, zinc was rapidly absorbed ($t_{1/2abs.}$=0.1040.02 h) by the alimentary system of birds attaining C_{max} of 63.603.94 mol/ml by hour 0.77 (compartmental method) and C_{max}=69.274.35 mol/ml by hour 0.92 h (non-compartmental method). It is characterized with a long biological half-life ($t_{1/2}$) of 13.821.63 h (compartmental analysis) and 15.961.73 h (non-compartmental analysis) and long mean residence times (MRT) 20.122.35 h and 23.002.50 h, respectively. The distribution in blood and extracellular fluid was good as seen from $Vd_{(area)}$ values 0.770.05 l/kg (compartmental analysis) and 0.650.05 l/kg (non-compartmental analysis).

Key words: pharmacokinetics, chickens, zinc aspartate

Introduction

Zinc is an essential mineral for plants, animals and microorganisms [1]. It has an effect on growth. Zinc is a cofactor of numerous enzymes (more than 300) involved in the synthesis and degradation of proteins, carbohydrates, lipids, as well as in synthesis and catabolism of RNA and DNA [2-4].

The major part of zinc in the organism of animals and men is found in the brain, muscles, bones, kidneys and liver, with highest concentrations in the prostate and eyes [5, 6].

It is included in the diets of poultry due to its essential role in a number of metabolic processes. In modern poultry industry, both organic and inorganic zinc compounds are utilised [7-9].

There is scientific evidence about difference in pharmacokinetics of organic and inorganic zinc compounds in different animal species [5, 10-16]. There is no information about zinc pharmacokinetics in poultry.

The purpose of the present research was to determine the pharmacokinetics of zinc after

intraingluvial application of zinc aspartate in broiler chickens.

Materials and Methods

In this pharmacokinetic study, 6 Cobb 500 broiler chickens (equal number of both genders), 45 days of age, weighing 1.5700.054 kg were included. The chickens were divided by gender in groups of 3 in metal cages at ambient temperature of 22-24C and air humidity 52%. They were fed compound food for growing birds and water was provided *ad libitum*.

The birds were treated with zinc aspartate, which represents an organic chelate complex of zinc synthesised in the Department of Organic Chemistry at the University of Chemical Technology and Metallurgy, Sofia. Due to the fact that the synthesised drug was insoluble in water, a 5% working suspension in 2% carboxymethyl cellulose was prepared *ex tempore.* Zinc aspartate was applied once, at a dose of 50 mg Zn/kg using an elastic silicone probe after 16-hour fasting.

Blood samples of 1 ml each were collected in Eppendorf tubes after venepuncture of the left wing *v. brachialis*. They were obtained on hour 0 (before treatment) and on post treatment hours 0.17, 0.33, 0.50, 1, 2, 4, 6, 8, 10, 12 and 24 h, left at room temperature for blood serum separation, centrifuged on a refrigerating centrifuge at 1500×*g* for 15 min. Separated sera were stored deep frozen at -18 C for 24 h. The assay of serum zinc concentrations was performed on a biochemical analyzer (BS-200, Mindray Co.) using a colorimetric assay at wavelength =560 nm. Test principle of the 5-Br-PAPS commercial kit consisted in the formation of coloured complex between zinc and [2-(5-Bromo-2-pyridiylazo)-5-[N-n-propyl-N-(3-sulfopropyl)amino]phenol,disodium]] whose colour intensity was proportional to the amount of zinc in the tested sample.

Using specialised pharmacokinetics software (TopFit, v.2.0.) [17] we determined zinc pharmacokinetics after intraingluvial application of zinc aspartate to broilers. Pharmacokinetic parameters of zinc behaviour after intraingluvial application were determined by the compartmental model [18] and by means of non-compartmental analysis [19]. With the former method, pharmacokinetic parameters were determined according to the Akaike information criterion (AIC) [20]. Pharmacokinetic parameters of zinc absorption, distribution and elimination were as follows: k_{el} elimination rate constant; $k_{abs.}$ absorption rate constant; $T_{1/2}$ biological half-life; $T_{1/2abs.}$ absorption half-life; MRT mean residence time; $Vd_{(area)}$ volume of distribution; T_{lag} hidden time; AUC_{0LOQ} area under the serum concentration-time curve from time zero to the limit of quantitation; AUC_0 area under the serum concentration-time curve from time zero to infinity; C_{max} maximum serum concentration; T_{max} time to reach C_{max}.

All pharmacokinetic values were presented as mean standard error of the mean (SEM).

Results

After single intraingluvial treatment with zinc aspartate, serum zinc concentrations were detected as early as the first sampling of blood in all birds (0.17 h) (Table 1).

Table 1. Serum zinc concentrations after oral treatment of broiler chickens with 5% zinc aspartate solution at a dose of 50 mg Zn/kg of body weight

Time interval (h)	Mean	SEM
0.17	20.783	1.699
0.33	43.233	2.404
0.50	54.817	3.717
1	60.233	4.418
2	68.983	4.399
4	60.117	3.491
6	49.817	2.336
8	46.367	2.267
10	42.517	1.909
12	38.683	1.626
24	34.483	1.593

The follow-up of individual serum curves in broiler chickens showed that they fitted the one-compartmental open pharmacokinetic model.

The pharmacokinetic parameters after non-venous route of application determined by the compartmental method are presented in Table 2.

Pharmacokinetic parameters of zinc absorption from the gut of chickens after oral application of the zinc organic chelate complex are shown in Table 2 and include the time for its appearance in blood or hidden time (t_{lag}) and absorption half-life ($T_{1/2abs.}$). Using both pharmacokinetic models (compartmental and non-compartmental analysis), maximum serum concentrations (C_{max}) of zinc were high and were attained soon after the intraingluvial application of zinc aspartate (Table 2).

After absorption, zinc was rapidly distributed in blood ensuring high values of the areas under the serum concentration-time curves (AUC_0; AUC_{0LOQ}).

Table 2 also presents pharmacokinetic parameters characterising the residence and elimination of zinc MRT and $T_{1/2}$. It could be seen that biological half-life and mean residence time of zinc after intraingluvial application of the chelate complex were long.

Table 2. Pharmacokinetic parameters of zinc after single oral treatment of broiler chickens with 5% zinc aspartate solution at a dose of 50 mg Zn/kg of body weight

Parameter	Units	Compartmental analysis		Non-compartmental analysis	
		Mean	SEM	Mean	SEM
$T_{1/2abs.}$	h	0.104	0.015	-	-
$T_{lag.}$	h	0.039	0.020	-	-
$T_{1/2\beta}$	h	13.82	1.629	15.96	1.730
MRT	h	20.12	2.352	23.000	2.503
$Vd_{(area)}$	l/kg	0.773	0.051	0.647	0.050
$AUC_{0\rightarrow LOQ}$	μmol x h/l	-	-	847.062	59.262
$AUC_{0\rightarrow\infty}$	μmol x h/l	1280.00	98.691	1211.837	225.354
T_{max}	h	0.767	0.073	0.917	0.083
C_{max}	μmol /l	63.600	3.941	69.267	4.346
r^2	-	-	-	0.974	0.003

Discussion

After intraingluvial treatment with zinc aspartate, serum concentrations of zinc were detectable in all blood samples from hour 0.17 to hour 24, similar to results from a previous study of ours on broilers treated with the organic compound zinc methionate at the same dose and concentration [21].

After application of zinc aspartate, serum zinc curves of all birds fitted the one-compartmental open pharmacokinetic model comparable to data reported for broilers by other researchers [8, 21] but differed from data registered in rats [5], rabbits [22, 23], fish [24], and humans [25] which fitted the two-compartmental pharmacokinetic model.

Data from Table 2 referring to the absorption half-life ($T_{1/2abs.}$) indicated that, in chickens, organic zinc was rapidly absorbed and consequently, maximum serum concentrations were rapidly attained. A similar tendency was established in an earlier study of ours in broiler chickens treated intraingluvially with another organic zinc compound – zinc methionate, applied at the same dose [21]. Unlike chickens, dogs treated orally with the zinc compound at 1 mg/kg exhibited twice longer T_{max} (T_{max}=2 h) [26]. A similar trend for more time needed for maximum serum concentrations were reported in humans by Nève, J. et al. (1991) T_{max}=2.3 h and in rabbits (T_{max}=1.33 h) [5].

After its occurrence in blood, zinc was rapidly distributed in the extracellular fluid and tissues with apparent volume of distribution $Vd_{(area)}$ 0.773 and 0.647 l/kg as per the two pharmacokinetic models, respectively (Table 2).

The pharmacokinetic profile of zinc after

single intraingluvial application of zinc aspartate is characterised with long-term residence of zinc in blood serum of broiler chickens, as indicated by biological half-life ($T_{1/2}$) and mean residence time (MRT) values as per the two used models (Table 2). $T_{1/2}$ and MRT values of zinc aspartate in broiler chickens were comparable to those reported by Ivanova, S. et al. (2014)[21] after single application of zinc methionate in the crop ($T_{1/2}$=15.45 h; MRT=22.50 h). Unlike chickens, the biological half-life of zinc in fish was considerably longer ($T_{1/2}$=16 days) as was the mean residence time (MRT=21 days) [24].

Conclusion

From the results obtained it can be concluded that zinc in the form of organic chelate complex is rapidly absorbed, which is a prerequisite for rapid maximal serum concentrations of the metal. Zinc is rapidly distributed in the extracellular fluid and tissue in large volume, providing temporally for a high area under the curve of serum concentration-time (AUC_0).

The serum pharmacokinetic profile shows monoexponential presentation and is characterized by long biological half-life ($T_{1/2}$) and mean residence time (MRT), which explain the delayed elimination of zinc from the body of the birds.

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