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# PHARMACOKINETICS OF IRON METHIONATE IN BROILER CHICKENS

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**ABSTRACT**
Tests to determine the pharmacokinetics of the iron methionate after single intravenous and intraingluvial treatment of broiler chickens at a dose of 10 mg / kg were made. The serum concentrations of the iron in both modes of administration were determined through the spectrophotometric method. Certain serum concentrations of the iron in both modes of administration were found within 12 hours after the treatment.

**Key words:** iron methionate, pharmacokinetics, chickens

## INTRODUCTION

Iron is an essential component of every cell in the body. It has a critical role in the transport and storage of oxygen i.e. hemoglobin and myoglobin. Within a large variety of enzymes iron acts as a catalyst for oxygenation, a necessity for the cellular growth. Iron supplements are administered to treat iron deficiency anemia, without a sufficient supply of iron, hemoglobin cannot be synthesized (1).

About 60 % of iron is found in the erythrocytes within hemoglobin (2), the oxygen transport protein. Most stored iron is in the form of ferritin; found in the liver, spleen, muscles and bone marrow. The relationship between the physiological iron compartments is very dynamic (3).

There is no information on the pharmacokinetics of iron and iron compounds in animals and especially in birds. The purpose of this study was to determine the pharmacokinetics of iron after intravenous and intraingluvial administration of iron methionate in broiler-chickens.

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## MATERIAL AND METHODS

Six Anglo-American broiler chickens – four of them linear hybrid ROSS-IKOV - equal in number of both genders, at the age of 35 - 45 days, weighing 1, 140 - 1, 380 kg were involved in this test. The birds were bred at a temperature of 25-26° C and air humidity of 50 %. The broilers were fed with pelleted fodder for growing birds. Their water was provided *ad libitum*.

We were kindly provided with the iron methionate substance by the Organic Chemistry Department at the University of Chemical Technology and Metallurgy, city of Sofia. It was produced by the interaction of geometionin and ferrous sulphate hydrate in water environment. We used the substance to prepare *ex tempore* working solution in a concentration of 1 %. There was 20-day "wash-out" period between the two modes of administration of iron methionate solutions for "cleansing" the body of the applied iron compound. We injected intravenously the iron methionate in the vein (*v. brachialis*) of the right wing and made venipuncture of the same

vein on the left wing to take blood. The intraingluvial administration of the iron methionate aqueous solution was made directly into the crop through an elastic silicone tube and syringe after 16 hour starvation diet. The blood samples (each of them 1 mL) were received in Eppendorf tubes at 0, 0.17, 0.33, 0.50, 1, 2, 4, 6, 8, 10, 12 and 24 hours after the treatment. We left the blood samples at a room temperature for 2 hours, then centrifuged them at 1500 rpm for 15 min for complete separation of the serum and stored them at a temperature of -20° C until the beginning of the analysis.

The content of the iron in the blood serum was determined through the spectrophotometric method with bioanalizator.

The pharmacokinetic modelling was done by using two methods – compartmental and non-compartanmental analysis (4). For this purpose we used the computer program TopFit, v. 2.0. The pharmacokinetic parameters were determined in accordance with the criterion of Akaike (5).

**RESULTS**

The mean serum concentrations of iron methionate after single intravenous (*i.v.*) and intraingluvial (*i. ingl.*) application of 1 % iron methionate aqueous solution are presented in **Table 1.** Serum concentrations of iron methionate above the initial values were found in all chickens within 12 hours after the birds were applied both methods of treatment.

***Table 1.*** *Serum concentrations of iron methionate as 1 % solution after single i.v. and intraingluvial treatment of chickens (Mean±SEM)*

| | **Intraingluvial administration** | | **Intravenous injection** | |
|---|---|---|---|---|
| **(h)** | Mean | SEM | Mean | SEM |
| **0.17** | 24.538 | 1.405 | 185.025 | 12.238 |
| **0.33** | 27.138 | 2.099 | 150.588 | 11.656 |
| **0.50** | 26.788 | 2.422 | 127.963 | 12.846 |
| **1** | 25.175 | 2.195 | 111.925 | 14.324 |
| **2** | 23.888 | 2.001 | 90.425 | 10.067 |
| **4** | 21.188 | 1.828 | 66.200 | 10.732 |
| **6** | 19.275 | 1.595 | 42.963 | 6.111 |
| **8** | 16.988 | 1.552 | 29.938 | 4.095 |
| **10** | 14.613 | 1.345 | 21.638 | 2.915 |
| **12** | 13.575 | 0.989 | 18.888 | 2.253 |

The iron methionate serum concentration curves at the *i.v.* injection of the birds corresponded to the two-compartmental pharmacokinetic model and those obtained at the intraingluvial administration – to the compartmental open model.

After the intravenous injection of iron methionate in the broiler chickens, the values of distribution half-life time ($T_{1/2\alpha}$) showed that the organic compound injected was distributed rapidly in the bird body **(Table 2)**.

The pharmacokinetic parameters corresponding to the level of distribution of the iron methionate in the body – the volume of distribution in the central compartment (Vc), the volume of distribution in the tissue compartment ($V_t$), the volume of distribution ($Vd_{(area)}$) and the steady state volume of distribution ($V_{ss}$) – had average values, which indicated its poor distribution into the bird body, and amounted to 0, 0028 L/kg, 0, 090 L/kg, 0,104 L/kg and 0,092 L/kg **(Table 2)**, respectively.

The values of $K_{12}$ and $K_{21}$ and the ratio $K_{12}/K_{21}$ showed more rapid movement of the iron from the central to the tissue compartment and the slower return of the iron ions from the tissue to the central compartment **(Table 2)**.

The biological half-life ($T_{1/2\beta}$) of the iron methionate determined by the compartmental method was significantly longer than that determined by the non-compartanmental

method **(Table 2)**. There was a similar trend in the mean residence time (MRT), which was determined by using both pharmacokinetic methods **(Table 2)**.

***Table 2.*** *Pharmacokinetic parameters of iron methionate after single i.v. injection of chickens with 1 % solution (Mean±SEM)*

| Parameter | Units | Compartmental analysis | | Non-compartmental analysis | |
|---|---|---|---|---|---|
| | | *Mean* | SEM | Mean | SEM |
| $K_{12}$ | $h^{-1}$ | 12.413 | 0.219 | - | - |
| $K_{21}$ | $h^{-1}$ | 0.4914 | 0.078 | - | - |
| $K_{el}$ | $h^{-1}$ | 1.6818 | 0.212 | - | - |
| $K_{12}/K_{21}$ | - | 33.619 | 8.615 | - | - |
| $T_{1/2\alpha}$ | h | 0.381 | 0.125 | - | - |
| $T_{1/2\beta}$ | h | 8.978 | 1.367 | 3.913 | 0.282 |
| $V_c$ | L/kg | 0.0028 | 0.0003 | - | - |
| $V_t$ | L/kg | 0.090 | 0.025 | - | - |
| $V_{ss}$ | L/kg | 0.092 | 0.020 | 0.034 | 0.004 |
| $Vd_{(area)}$ | L/kg | 0.104 | 0.021 | 0.039 | 0.005 |
| MRT | h | 11.856 | 1.790 | 5.451 | 0.414 |
| $AUC_{0\rightarrow\infty}$ | mmol.h/L | 1268.38 | 187.07 | 770.276 | 82.995 |

The intraingluvial administration of iron methionate showed that the iron was absorbed rapidly by the digestive tract of the chickens. This was proved by the values of the absorption half-life time ($T_{1/2abs.}$) and those of the mean absorption time (MAT) **(Table 3)**.

The biological life ($T_{1/2\beta}$) of the iron determined by both pharmacokinetic methods was evidence about its longer stay in the chicken body compared to the intravenous injection. There was a similar trend in the mean residence time (MRT), where the MRT values at the intraingluvial administration were approximately twice higher than those found at the intravenous injection of the product.

The maximum serum concentrations ($C_{max}$) of the iron – 26, 350 and 28, 938 mmol/L, respectively were reached relatively quickly ($T_{max}$ = 0,450 h and 0,563 h) after the intraingluvial administration of iron methionate **(Table 3)**.

The determined values of the absolute bioavailability of the iron (F = 25.314 and 35.109 %) showed relatively good bioavailability in this non-intravenous mode of administration **(Table 3)**.

***Table 3.*** *Pharmacokinetic parameters of iron methionate after single intraingluvial treatment of broiler chickens with 1% solution (Mean±SEM)*

| Parameter | Units | Compartmental analysis | | Non-compartmental analysis | |
|---|---|---|---|---|---|
| | | Mean | SEM | Mean | SEM |
| $T_{1/2\beta}$ | h | 12.548 | 3.010 | 14.359 | 2.265 |
| $T_{1/2abs.}$ | h | 0.420 | 1.458 | - | - |
| MRT | h | 21.310 | 3.744 | 20.663 | 3.279 |
| $AUC_{0\rightarrow\infty}$ | mmol. h/L | 544.25 | 77.755 | 532.713 | 68.580 |
| $T_{max}$ | h | 0.450 | 0.046 | 0.563 | 0.211 |
| $C_{max}$ | mmol/L | 26.350 | 1.777 | 28.938 | 2.028 |
| MAT | h | 1.463 | 0.486 | 3.539 | 0.589 |
| F | % | 25.314 | 6.606 | 35.109 | 4.381 |

## DISCUSSION

There are no studies about the pharmacokinetics of the iron in broiler chickens and therefore we may do a comparison with the data set for other animal species and humans. The information about the pharmacokinetics of the iron in pigs injected intravenously with iron methionate at a dose of 20 mg/kg is of interest in the literature. The maximum serum concentrations ($C_{max}$ = 26. 350 mmol/L and $C_{max}$ = 28, 938 mmol/L), which we determined in the chickens by using the two pharmacokinetic methods, were significantly lower than those determined by Petrichev M. (6) in pigs treated with iron methionate – $C_{max}$ = 104,50 mmol/L, which we could explain with the five times higher dose (50 mg/kg) used in the pigs. The ratio in the values of $T_{max}$ ($T_{max}$ = 0.45 h and $T_{max}$ = 0.563 h) observed in the broiler chickens was similar, compared to those in the pigs determined by Petrichev M. (6) – $T_{max}$ = 2.67. The biological half-life ($T_{1/2\beta}$) and the mean residence time (MRT) after intravenous injection in broiler chickens had lower values compared to those in the pigs ($T_{1/2\beta}$ = 9.41 h and MRT = 13.56 h) after intravenous injection with iron methionate (6).

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