Pharmacokinetics and Bioavailability of Thiamphenicol After A Single Intravenous and Oral Administrations in Broiler Chickens

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ABSTRACT

The pharmacokinetic profile of thiamphenicol was studied in broiler chickens following a single intravenous (IV) and oral (PO) administration at dosage rate 30 mg/kg BW. Serum concentrations of TP were determined by high performance liquid chromatography (HPLC). After IV dose, the serum thiamphenicol concentration time course was found to obey two-compartment open model. After IV dose, elimination half-life (t1/2λz), volume of distribution at steady state (Vdss), total body clearance (Cltot) and mean residence time (MRT) of TP were 4.58±0.2hr, 2.31±0.1L/kg, 0.31±0.006L/hr/kg, and 2.44±0.1hr, respectively. After oral administration of thiamphenicol, the peak plasma concentration (Cmax) was 14.58±0.1μg/ml and was obtained at 3.64±0.01hr (tmax) post administration. Elimination half-life (t1/2el) and absorption half-life t1/2ab.) were 2.65±0.01hr and 2.06±0.01hr, respectively. The systemic bioavailability following oral administration of TP was 117.79±1.2%. TP therapy with dosage rate of 30 mg/kg BW is suggested for a beneficial clinical effect in broiler chickens.

Keywords: Pharmacokinetics, Broiler chickens, Thiamphenicol

INTRODUCTION

Thiamphenicol (TP), is a broad-spectrum bacteriostatic antibiotic. Its mode of action is binding to the 50S ribosomal subunit leading to inhibition of the activity of peptidyltransferase, resulting in embarrasment of bacterial protein synthesis (Dowling, 2013; Tikhomirov et al., 2019).

Thiamphenicol is similar in its structure to chloramphenicol (CP), but the main dissimilarity between thiamphenicol and chloramphenicol is that the sulfomethyl group replaces p-nitro group (Switala et al., 2007).

Unlike chloramphenicol, thiamphenicol and florfenicol were not stated to result in aplastic anemia (Yunis and Gross, 1975) due to absences of the p-nitro group which is considered as the cause of chloramphenicol’s severe undesirable effects (Branger et al., 2004). Thiamphenicol has been used in veterinary medicine as a substitute for chloramphenicol, which was banned from use in food producing animals.

Thiamphenicol is used in a broad spectrum of infections caused by Gram +ve and Gram –ve bacteria in poultry (Switala & Debowy, 2005; Switala et al., 2007; Wei et al., 2016).

There are a limited literatures on pharmacokinetics of thiamphenicol in poultry as in broiler chickens (Chen & Pu, 2008), turkeys (Kowalski, 2007; Switala et al., 2007), and ducks (Tikhomirov et al., 2019), quails (Aboubakr & Soliman,2020) and geese (Tikhomirov et al., 2020). The data available about thiamphenicol pharmacokinetics in broiler chickens in adequate. Therefore, this paper was aimed to study the pharmacokinetics of thiamphenicol and its bioavailability after single IV and oral doses in broiler chickens.

MATERIALS AND METHODS

Drug

Thiamphenicol was obtained as an oral solution 25% under trade name of (Atothiacol)® from ATCO Pharma Co., Egypt. Each 1ml contains 250 mg thiamphenicol.
**Experimental birds**
Six apparently healthy Arbor Acres broiler chickens of both sexes ranging in their weight from 1000-1200 g. were used. The chickens were purchased from a poultry farm house, kept in hygienic floor and were fed on well-adjusted antimicrobial free ration and water was accessible to chickens as ad-libitum. Chickens were kept under observation for 2 weeks before the beginning of experiments to confirm that chickens body fluids and tissues were free from the drug residues.

**Experimental design**
Each chicken was weighed separately to calculate the dose of thiamphenicol before its administration. Chickens were given thiamphenicol as a single IV dose into the left-wing vein at a dosage of 30 mg/kg BW (Switała et al., 2007). After an interval of 2 weeks, chickens were received the same dose of thiamphenicol orally. Blood samples of 1ml (0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours) after oral and intravenous administration have been obtained from the wings of each bird. Blood samples were put in slop position to coagulate at ordinary temperature; then centrifuged at 3000 r.p.m for 15 minutes. The resultant serum samples were stored in sterile plastic eendorff tubes at -20°C until examined.

**Analytical method**
Thiamphenicol serum concentrations were measured using HPLC (Agilent, USA) according to (Switała et al., 2007). The column used was C18 (5 mm, 250 mm, C18 4.6 mm) for chromatographic separation (USA). The column temperature was held at 40°C. The mobile phase consisted of a combination of acetonitrile and water in isocratic form (18:82). This mixture inflated into HPLC using a low-pressure gradient system. The period for retention was 5.2 min. A wavelength of 225.3 nm was fixed for ultraviolet-visible detection.

Validation of the TP assay suggested a detection limit (LOD) of 0.01μg/mL, quantification limit (LOQ) of 0.03 μg/mL. Thiamphenicol's calibration curve was linear between 0.1 and 50μg/ml.

**Pharmacokinetic analysis**
The determination of the best-fit compartmental model and the estimation of the model-dependent pharmacokinetic parameters were made with the help of a computerized curve- stripping program (R-strip, Micromath Scientific Software, Salt Lake City, UT, USA). All pharmacokinetic parameters were estimated on the basis of Baggot, (1978). According to Snedecor and Cokran (1980), the mathematical study was carried out.

**RESULTS**
The mean serum concentration–time profile of thiamphenicol was shown in the figure (1) after a single intravenous (IV) and oral (PO) administration of 30 mg/kg BW. Thiamphenicol could be detected in serum for 24 hours. The pharmacokinetic parameters of thiamphenicol were shown in table (1). After i.v. administration, the data on thiamphenicol serum concentration period was based on the two-compartment open model. The distribution half-life (t0.5(α)) was 0.58 ± 0.01 and the elimination (t0.5(β)) half-life was 4.58 ± 0.2h. Total body clearance (CiB) was 0.31 ± 0.006 L kg⁻¹ h⁻¹, steady state volume of distribution (Vdss) was 2.31 ± 0.1 L kg⁻¹, and mean residence time was 2.44 ± 0.1h. Thiamphenicol was absorbed rapidly after oral administration with half-life absorption (t 0.5(ab)) 2.06 ± 0.01 h. The peak serum concentration (Cmax) was 14.58±0.1μg ml⁻¹ at a maximum period (tmax) of 3.64±0.01 hours after administration. The systemic bioavailability after oral administration was 117.79 ± 1.2 %.
**DISCUSSION**

Our findings demonstrated that the thiamphenicol serum concentration injected IV into broilers follows a model of two open compartments. This result was agreed with those formerly documented in rabbit (Abd El-Aty et al., 2001), calves & lambs (Mengozzi et al., 2002), broiler chickens (Chen and Pu, 2008), male goats (Bogzil and Tohamy, 2015), and florfenicol (FF) in pig (Liu et al., 2003). Longer half-life of distribution was recorded for florfenicol in sheep 1.51 ± 0.06 h (Jianzhong et al., 2004).

Following a single intravenous administration, the half-life of distribution of thiamphenicol was nearly similar to that formerly described for FF in pig 0.37 h (Liu et al., 2003), FF in buffalo calves 0.381 ± 0.004 h (El-Gendy et al., 2005) and TP in broiler chickens 0.27±0.02 h (Chen and Pu, 2008). The distribution half-life of thiamphenicol was nearly similar to that formerly described for FF in pig 0.37 h (Liu et al., 2003), FF in buffalo calves 0.381 ± 0.004 h (El-Gendy et al., 2005) and TP in broiler chickens 0.27±0.02 h (Chen and Pu, 2008).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>I.V. Parameter</th>
<th>Unit</th>
<th>P.O.</th>
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<tr>
<td>Cpo</td>
<td>ug ml-1</td>
<td>86.19±0.2</td>
<td>kab</td>
<td>h-1</td>
</tr>
<tr>
<td>A</td>
<td>ug ml-1</td>
<td>82.25±0.2</td>
<td>Kel</td>
<td>h-1</td>
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<tr>
<td>B</td>
<td>ug ml-1</td>
<td>4.11±0.4</td>
<td>t0.5(ab)</td>
<td>h</td>
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<tr>
<td>α</td>
<td>h-1</td>
<td>1.18±0.02</td>
<td>t0.5(el)</td>
<td>h</td>
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<tr>
<td>β</td>
<td>h-1</td>
<td>0.15±0.01</td>
<td>Cmax</td>
<td>ug ml-1</td>
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<td>k21</td>
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<td>0.20±0.01</td>
<td>tmax</td>
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<tr>
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<td>h-1</td>
<td>0.89±0.01</td>
<td>AUC</td>
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<td>1.14±0.01</td>
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<td>h</td>
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<tr>
<td>t0.5(α)</td>
<td>h</td>
<td>0.58±0.01</td>
<td>F</td>
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<tr>
<td>t0.5(β)</td>
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<td>4.58±0.2</td>
<td>MRT</td>
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<tr>
<td>AUC</td>
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<td>Vc</td>
<td>L kg-1</td>
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<td>Vdss</td>
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<tr>
<td>CIB</td>
<td>L kg-1 h-1</td>
<td>0.31±0.006</td>
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Aboubakr, 2019). Moreover, this result is shorter than thiamphenicol (5.5 h) in preruminant calf (Intorre et al., 1997).

The systemic bioavailability of thiamphenicol following its single oral dose in control chickens was (117.79± 1.2%) which almost the same as oral bioavailability of TP in pig 112.9% (Liu et al., 2003), florfenicol in broiler chickens 94% (Shen et al., 2003), florfenicol in dog 95.43% (Park et al., 2008), but higher than values recorded for thiamphenicol in turkeys 68.24 % (Switała et al., 2007), thiamphenicol in quails (78.10%) (Aboubakr and Soliman 2020), florfenicol in ducks 73.86% (Tikhomirov et al., 2019). Moreover, this result is lower than that of TP in chickens 138.58% (Chen and Pu, 2008).

The absorption half-life (T0.5(ab)) was 2.06 ± 0.01 h. Our result was similar to that recorded for florfenicol (2.05 hr) in turkeys (Switała et al., 2007). Moreover, this result is shorter than thiamphenicol (4.58 hr), and chloramphenicol (4.95 hr) in turkeys (Switała et al., 2007) but longer than florfenicol (1.55 hr) in ducks (Tikhomirov et al., 2019) and TP in quails (1.56 hr) (Aboubakr and Soliman 2020).

The elimination half-life (T0.5(ab)) of thiamphenicol was (2.65±0.01 h.). This result was like to those described for FF in ducks 2.77 hr (Tikhomirov et al., 2019). Moreover, this value was longer than FF in dog 1.24 h (Park et al., 2008), FF in rabbit 2.35h (Park et al., 2007) Furthermore, this value was shorter than florfenicol in Muscovy ducks 7.41 hr (El-Banna, 1998), thiamphenicol in turkeys 7.40 hr (Kowalski, 2007) and thiamphenicol in quails (4.01 hr) (Aboubakr and Soliman 2020).

CONCLUSIONS

Serum concentration of thiamphenicol in broiler chickens could be detectable in a therapeutic level for 24 h following oral administration. The mean systemic bioavailability of thiamphenicol following a single oral administration in normal broiler chickens was 117.79%. This reflex a good absorption of thiamphenicol after its oral dosing.
REFERENCES


