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Pharmacology

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 embarrassment 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 (Switała *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 chloramphhenicol, 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; Switała *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; Switała *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 ependorff 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 ($t_{0.5(\alpha)}$) was 0.58 ± 0.01 and the elimination ($t_{0.5(\beta)}$) half-life was 4.58 ± 0.2h. Total body clearance (ClB) 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 %.

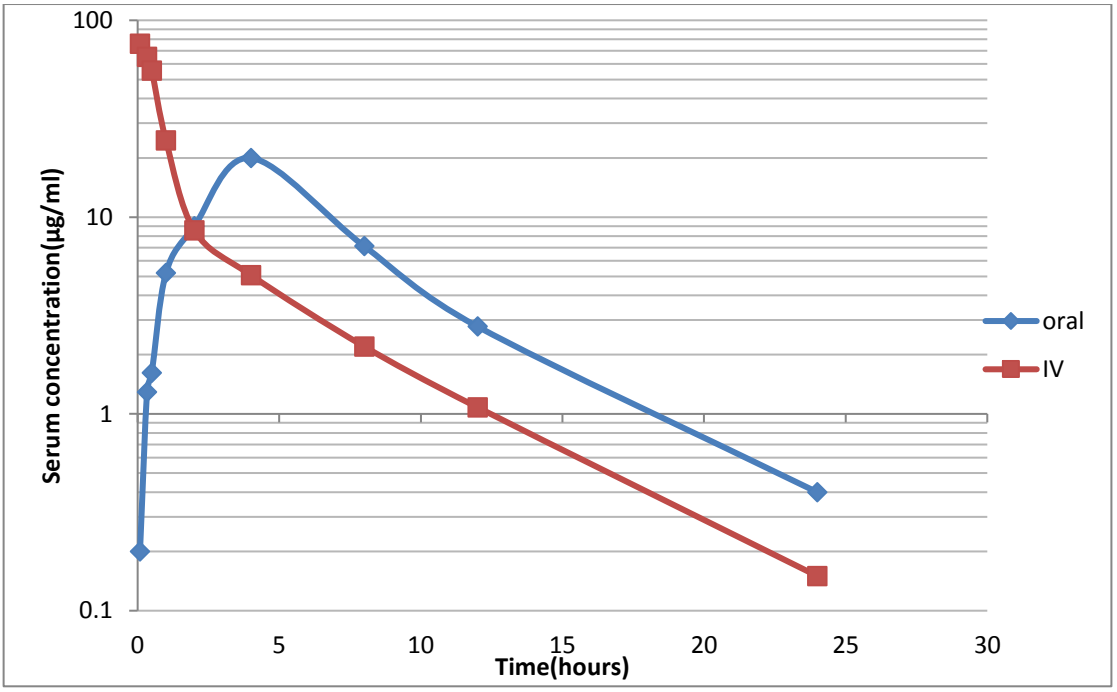

Fig. (1): Semi-logarithmic curve showing the time-concentration of thiamphenicol in chicken serum after single IV and PO administration of 30 mg/kg BW (n = 6).

Table (1) : Mean ± *SE* serum pharmacokinetic parameters of thiamphenicol in chickens following IV and PO administration of 30 mg/kg BW (n = 6).

Parameter	Unit	I.V.	Parameter	Unit	P.O.
Cpo	ug ml-1	86.19±0.2	kab	h-1	0.34±0.003
A	ug ml-1	82.25±0.2	Kel	h-1	0.26±0.001
B	ug ml-1	4.11±0.4	t0.5(ab)	h	2.06±0.01
α	h-1	1.18±0.02	t0.5(el)	h	2.65±0.01
β	h-1	0.15±0.01	Cmax	ug ml-1	14.58±0.1
k21	h-1	0.20±0.01	tmax	h	3.64±0.01
Kel	h-1	0.89±0.01	AUC	ug ml-1 h-1	132.67±0.9
k12	h-1	1.14±0.01	MRT	h	6.79±0.03
t0.5(α)	h	0.58±0.01	F	%	117.79± 1.2
t0.5(β)	h	4.58±0.2			
MRT	h	2.44±0.1			
AUC	ug ml-1 h-1	112.65±0.6			
Vc	L kg-1	0.34±0.002			
Vdss	L kg-1	2.31±0.1			
ClB	L kg-1 h-1	0.31±0.006			

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 & lambbs (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).

Following a single intravenous administration, the half-life of distribution of thiamphenicol (T1/2α) was very short (0.58±0.01h) in control birds. 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) . Longer half-life of distribution was recorded for florfenicol in sheep 1.51 ± 0.06 h (Jianzhong *et al.*, 2004).

The drug elimination half-life {t0.5(β)} was (4.58±0.2h) similar to those recorded in turkeys 4.19 hr (Kowalski, 2007). This result was extended than thiamphenicol in turkeys 1.71 hr (Switała *et al.*, 2007), chickens 2.16hr (Chen and Pu, 2008), ducks 1.96 hr (Tikhomirov *et*

al., 2019), quails 3.83 hr (Aboubakr and Soliman, 2020), geese 2.84hr (Tikhomirov *et al.,* 2020) and FF in pig 2.91 h (Liu *et al.,* 2003), FF in quails1.24 hr (Ismail *and* El-Kattan, 2009), FF in sheep 3.34hr (Birdane *et al.,* 2015) and FF in ducks 1.56 hr (Tikhomirov *et al.,* 2019) and smaller than Flofenicol7.17 hr in ducks (El-Banna,1998) and FF in chickens 6.38 hr (El Sayed *et al.,* 2016) .

Total body clearance of the drug was (0.31 L/kg/h). Similar findings have been reported for TP in turkeys 0.34 L/hr/kg (Switała *et al.,* 2007), FF in rabbit 0.34 L/kg/h. (Abd El-Aty *et al.,* 2004). In contrast, a higher clearance was recorded of FF in broiler chickens 1.02 L/hr/kg (Shen *et al.,* 2003) and TP in male goats 1.025L/hr/kg (Bogzil and Tohamy 2015). Moreover, lower clearance for TP was reported in ducks 0.26 L/kg/h. (Tikhomirov *et al.,* 2019), geese 0.23 l/h/kg (Tikhomirov *et al.,* 2020) and quails 0.19 L/hr/kg (Aboubakr and Soliman 2020).

In the present study, the Vdss was (2.31 L/kg). This value is agreed with those described for FF in dogs 1.19 l/kg (Birdane and Birdane 2015) and higher than data reported for TP in turkeys 0.83 L/kg (Switała *et al.,* 2007), Florfenicol in duck 0.58L/kg and Thiamphenicol in ducks 0.68 L/kg (Tikhomirov *et al.,* 2019) and TP in quail 0.84 L/kg (Aboubakr and Soliman, 2020) and lesser than those reported for FF in chickens 3.50 L/kg (Shen *et al.,* 2003) and FF in quails 4.70L/kg, in chickens 5.33L/kg, in pigeons5.76 L/kg (Ismail & El-Kattan, 2009) and FF in Japanese quail 8.7L/kg (Koc *et al.,* 2009) .

These differences may be attributed to different species, method of assay, the health and age of the animal (Haddad *et al.,* 1985).

Following single oral dose administration, the observed mean peak serum level of the drug in the current study (Cmax) was (14.58±0.1µg/ml), and this was similar to those documented for FF in rabbit 15.14 µg/ml (Abd El-Aty *et al.,* 2004)) and higher than thiamphenicol (8.99 µg/ml) in turkeys (Switała *et al.,* 2007), TP in male goats 6.89 µg/ml (Bogzil and Tohamy 2015) , FF in chickens 4.83 µg/ml (El Sayed *et al.,* 2016) but lower than those reported for TP in ducks 20.27 µg/ml (Tikhomirov *et al.,* 2019), geese 20.02µg/ml (Tikhomirov *et al.,* 2020) and quails 19.81 µg/ml (Aboubakr and Soliman, 2020).

Thiamphenicol reached to its maximum serum concentration (Tmax) after (3.64 h) which was nearly similar to those in turkeys 4.57 hr (Switała *et al.,* 2007) and longer than TP (1.42 hr) in turkeys (Kowalski, 2007), florfenicol (2.00 hr) in turkeys (Switała *et al.,* 2007) , florfenicol (1.53 h) in chickens **(**El Sayed *et al.,* 2016), thiamphenicol (2 hr) in quails (Aboubakr and Soliman, 2020). Moreover, this result is shorter than thiamphenicol (5.5 h) in preruminant calve (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 ($T_{0.5(el)}$) 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.

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