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Pharmacology

Influence of Toltrazuril on Disposition Kinetic and Bioavailability of Thiamphenicol in Broilers

Taha A. Attia, Saber A. EL Hanbaly, Eman El-Hoseiny*

Department of Pharmacology, Faculty of Veterinary Medicine, University of Sadat City.

**corresponding author: eman.elhoseiny@yahoo.com* *Received: 7/11/2020 Accepted: 20/12/2020*

ABSTRACT

The Effect of toltrazuril on the disposition kinetics and bioavailability of thiamphenicol following a single intravenous (IV) and oral administrations in broiler chickens at a dose of 30 mg/kg body weight was investigated. The serum thiamphenicol concentration was detected by high performance liquid chromatography. After IV injection, thiamphenicol serum concentration was best to be described by a two-compartment open model. Toltrazuril pretreatment was resulted in a significance increase in Vdss and Cltot (3.51±0.1and 0.38±0.005 L/kg, respectively) of thiamphenicol compared with thiamphenicol administered alone (2.31±0.1 and 0.31±0.006L /kg, respectively).The elimination half-life and the mean residence time of thiamphenicol were 4.58±0.2 and 2.44±0.1, 5.72±0.2 and 2.25±0.1h., in control and toltrazuril pretreated chickens, respectively. Following oral dosing, the maximum serum concentration was 14.58±0.1 and 11.88±0.04 µg/ml reached at 3.64±0.01 and 3.56±0.01h, in control and toltrazuril pretreated chickens, respectively. Oral bioavailability was found to be 117.79± 1.2 and114.85 ±0 .7 % in control and toltrazuril pretreated chickens, respectively. It was concluded that the pretreatment of toltrazuril with thiamphenicol in broilers altered the pharmacokinetic profile of thiamphenicol.

Keywords: *Toltrazuril – Thiamphenicol - Broilers-disposition kinetics*

INTRODUCTION

Kinetic disposition of drugs interactions had a significant importance in veterinary medicine. Concurrent usage of several drugs may give rise to DDIs that can lead to altered concentrations of drugs in the body, which can badly affect the treatment of diseases or human food safety. In pharmacokinetic interactions, one drug may change the effect of another one by altering its absorption, distribution, metabolism or excretion. Coccidiosis is a major dangerous disease in poultry production (Greif, 2000). Anti-coccidial drugs were the dominant means of prevention and control of coccidiosis (Greif et al., 2001). These establish a main problem for poultry production, since several combinations have typically been added as feed additives to poultry rations (Jones and Ricke, 2003) that can interfere with any taken drug. One of these combinations is anticoccidials; their clinical implementation varied significantly in poultry farms (Echman, 1997). Toltrazuril, is used in the prevention and cure of coccidiosis in turkeys and chickens (Vertommen et al., 1990). Till now, there is no data about DDIs of the kinetic profile between thiamphenicol and anticoccidial drugs in broilers are recorded. This work was aimed to evaluate the effect of toltrazuril on the pharmacokinetics of thiamphenicol in broilers.

MATERIALS AND METHODS

Drugs

Thiamphenicol was obtained as an oral solution 25% under trade name (Atothiacol)® from ATCO Pharma Co., Egypt. Each 1ml contains 250 mg thiamphenicol.

Toltrazuril was obtained as an oral solution 2.5% under trade name (Atocox)® from ATCO Pharma Co., Egypt. Each one ml contains 25 mg toltrazuril base.

Experimental birds

Twelve apparently healthy Arbor Acres broilers of both sexes weighing from 1000-1200 g. were used. Birds were purchased from a private farm house kept in sanitary floor system chambers

and were fed on well-adjusted antimicrobial free ration and water was accessible to chickens as *ad-libitum*. Birds were put under observation for 2 weeks before beginning of the experiments to confirm that chickens body fluids and tissues were free from the drug residues.

Experimental design

Each chicken was individually weighed to estimate the dose of thiamphenicol and toltrazuril before their administration. Six broilers orally pretreated by toltrazuril at a rate of 7 mg/kg b.wt once daily for two successive days (Soliman, 2015) and after the last dose by 2 hours, thiamphenicol was injected intravenously with a single dose of 30 mg/kg b.wt(Switała *et al.*, 2007) in the left wing vein. Birds were left for two weeks then, orally pretreated with toltrazuril at a dose of 7 mg/kg b.wt once daily for two consecutive days and after the last dose by 2 hours, each bird was given thiamphenicol orally at 30 mg/kg b.wt. The other six chickens were considered as control and were given thiamphenicol as a single IV dose into the left wing vein at a dosage of 30 mg/kg BW and after an interval of 2 weeks, these chickens were received the same dose of thiamphenicol orally. Blood sample (1ml), at 5,10, 20, 30 minutes and 1, 2, 4, 6, 8, 12, 24 hours were obtained from each bird's right-wing vein after i.v and oral dosing for determination of thiamphenicol concentration using HPLC method.

Blood samples were left in a slop position to clot, then centrifuged at 3000 r.p.m for 15 minutes. The resulting serum samples were kept in sterile plastic ependorff tubes at -20° C until assayed.

Analytical method

Serum concentrations of thiamphenicol were estimated 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 peroid 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

It was made with a computerized programme of curve stripping (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

Serum concentration-time curves of thiamphenicol in broilers after a single intravenous injection of 30 mg/kg b.wt., administered alone and / or pretreated with toltrazuril are shown in figure (1). The resultant kinetic parameters are tabulated in table (1). The serum concentration-time curves of thiamphenicol in broilers after a single oral administration of 30 mg.kg-/ b.wt., administered alone and / or pretreated with toltrazuril are illustrated in figure (2). The corresponding kinetic parameters are illlustrated in table (2).

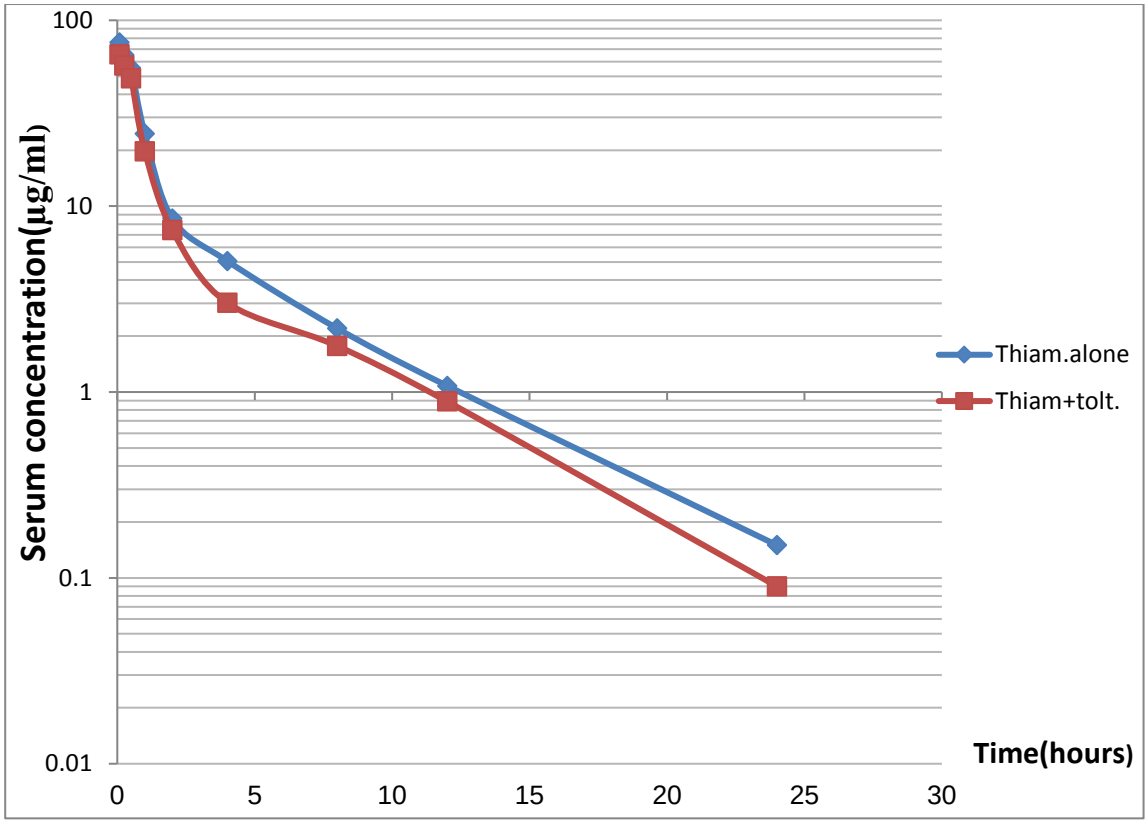

Fig. (1): Semilogarithmic graph depicting the time course of thiamphenicol in the serum of broilers after a single intravenous injection of 30 mg/kg.b.wt. alone and/or pretreated with toltrazuril.

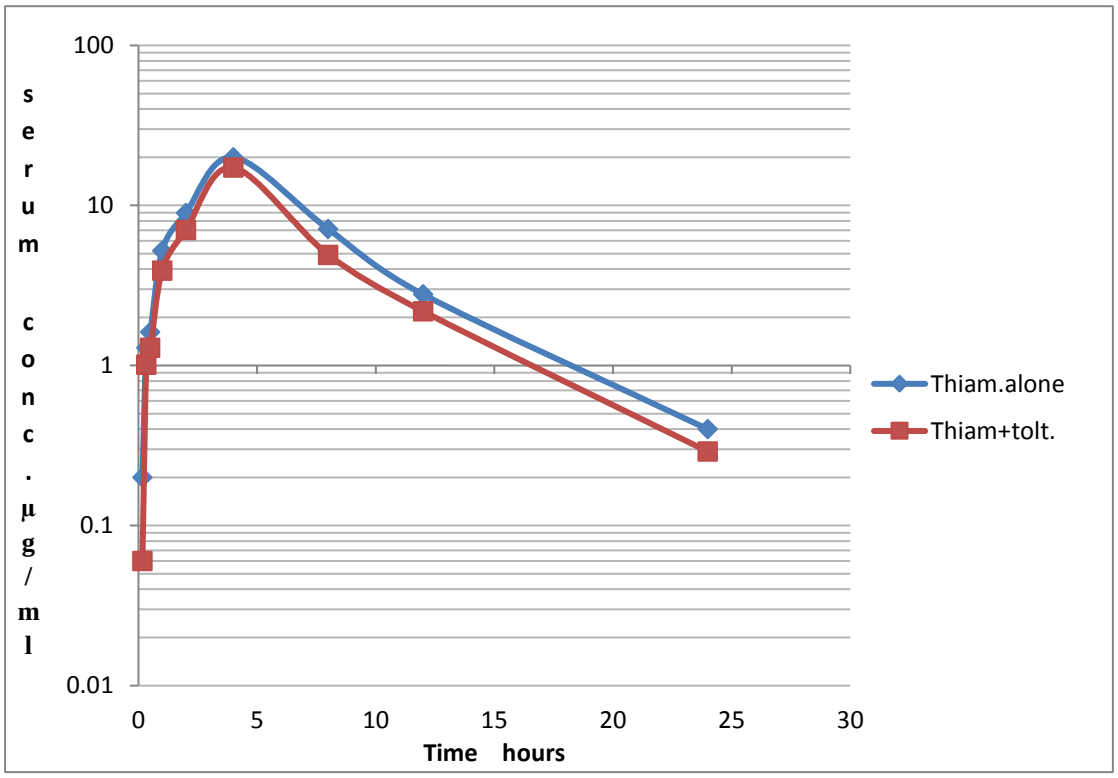

Figure (2): Semilogarithmic graph depicting the time course of thiamphenicol in serum of broilers after a single oral dose of 30 mg/kg.b.wt. alone and/or pretreated with toltrazuril.

Table (1): Mean pharmacokinetic parameters of thiamphenicol in broilers after a single intravenous injection of 30 mg.kg-1 b.wt. alone and /or pretreated with toltrazuril orally at a dose rate of 7mg/kg.bw.

Parameter	Units	X ± S.E.	
		Thiamphenicol I.V.	Thiamphenicol I.V. + Toltrazuril P.O.
C_o	$\mu g.ml^{-1}$	86.19±0.2	75.13±0.1***
A	$\mu g.ml^{-1}$	82.25±0.2	73.33±0.2***
α	h^{-1}	1.18±0.02	1.16±0.007
$T_{0.5(\alpha)}$	h	0.58±0.01	0.59±0.004
B	$\mu g.ml^{-1}$	4.11±0.4	1.80±0.1***
β	h^{-1}	0.15±0.01	0.12±0.006
$T_{0.5(\beta)}$	h	4.58±0.2	5.72±0.2**
$AUC_{(0\text{-}inf)}$	$\mu g.h.ml^{-1}$	112.65±0.6	92.16±0.9***
MRT	h	2.44±0.1	2.25±0.1
K12	h	1.14±0.01	1.14±0.006
K21	h	0.20±0.01	0.14±0.006
K_{el}	h^{-1}	0.89±0.01	0.98±0.01***
$V_{d\beta}$	L/kg	7.81±0.9	17.49±1.7***
V_c	L/kg	0.34±0.002	0.39±0.002
V_{darea}	L/kg	2.08±0.1	3.17±0.1***
V_{dss}	L/kg	2.31±0.1	3.51±0.1***
Cl_{tot}	L/kg/hr	0.31±0.006	0.38±0.005***

Table (2): Mean pharmacokinetic parameters of thiamphenicol in broilers after a single oral administration of 30 mg.kg-1 b.wt. alone and /or pretreated with toltrazuril orally at a dose rate of 25 ppm.

Parameter	Units	X ± S.E.	
		Thiamphenicol P.O.	Thiamphenicol P.O. + Toltrazuril P.O.
A	$\mu g.ml^{-1}$	159.21±3.08	71.83 ± 2.1***
K_{ab}	h^{-1}	0.34±0.003	0.38±0.003***
$T_{0.5(ab)}$	h	2.06±0.01	1.81±0.01***
B	$\mu g.ml^{-1}$	159.21±3.08	71.83±2.1***
K_{el}	h^{-1}	0.26±0.001	0.24±0.002
$T_{0.5(el)}$	h	2.65±0.01	2.87±0.01***
C_{max}	$\mu g.ml^{-1}$	14.58±0.1	11.88±0.04***
T_{max}	h	3.64±0.01	3.56±0.01***
$AUC_{(0\text{-}inf)}$	$\mu g.h.ml^{-1}$	132.67±0.9	105.83±0.9***
MRT	h	6.79±0.03	6.76±0.021

DISCUSSION

Current studies revealed that co-administration of a number of anthelmintics (ivermectin, albendazole and rafoxanide) with florfenicol in goats (Atef *et al.,* 2010) and supplementation of some polyether ionophore anticoccidial drugs (salinomycin, monensin and maduramycin) as feed additives in broilers (Wang *et al.,* 2013) can change the disposition kinetics of florfenicol. So far, little is recognized about whether the use of anticoccidial drugs as toltrazuril can affects the kinetic profile of thiamphenicol in broilers.

The current study revealed that, serum concentration of thiamphenicol after intravenous injection ($30mg.kg^{-1}$) in control broilers and those pre-treated with toltrazuril followed a two-compartment open model. This result was similar to those formerly documented in FF with albendazole in goats (Atef *et al.*, 2010) and FF with polyether ionophore antibiotics in broilers (Wang *et al,.* 2013).

The serum concentration of thiamphenicol in toltrazuril pretreated chickens is significantly decreased at various time intervals following IV administration. These results showed a low C0 value (75.13±0.1µg/ml) in toltrazuril pretreated chickens compared to values of control birds (86.19±0.2µg/ml). This result was similar to co-administration of florfenicol with SAL, MON, or MAD in broilers (Wang *et al.* 2013). Also, administration of amprolium with amoxicillin resulted in a significant reduction in C max compared with amoxicillin alone (El-Sayed *et al.,* 2014).

Following a single intravenous administration, the half-life of distribution (T1/2α) was very short (0.58±0.01h) in control birds. The distribution half-life of thiamphenicol was closely similar to that previously recorded for Florfenicol 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 broilers (t1/2α 0.27±0.02

h, Chen & Pu 2008).Longer half-life of distribution was recorded for florfenicol in sheep (1.51±0.06 h, Jianzhong *et al.,* 2004).The distribution half-life time (t½α) in toltrazuril pretreated broilers was (0.59±0.004h.) compared to control broilers (0.58±0.01h).

In control broilers, the elimination half-life of thiamphenicol was (4.58h) nearly parallel to that previously reported for thiamphenicol in turkeys (4.19 hr, Kowalski, 2007) , chloramphenicol in cow (4.2h, Anderson *et al.,* 1983) and thiamphenicol in calves (3.76hr, Intorre *et al.,* 1997). Moreover, the T1/2 of elimination reported in the present study (4.58±0.2h) was longer to that reported for thiamphenicol in turkeys (1.71 hr, Switała *et al.,* 2007), thiamphenicol in chickens (2.16 hr, Chen & Pu, 2008), but it was lower than florfenicol elimination half-life in Muscovy ducks (7.17 hr, El-Banna,1998) and florfenicol in chickens (6.38 hr, El Sayed *et al.,* 2016). In this study, the elimination half- life time of thiamphenicol in chickens pretreated with toltrazuril was found to be 5.72±0.2h longer than control ones (4.58±0.2h).

The total body clearance of thiamphenicol in this study (0.31 L/kg/h.) was higher than those described formerly for thiamphenicol in ducks (0.26 L/kg/h,. Tikhomirov *et al.,* 2019), thiamphenicol in geese (0.23 l/h/kg, Tikhomirov *et al.,* 2020) and thiamphenicol in quails (0.19 L/hr/kg, Aboubakr and Soliman, 2020). The total body clearance of thiamphenicol in control chickens recorded in this study (0,31 L/kg/h.) was slightly less than the value recorded in toltrazuril pre-treated birds (0.38±0.005 L/kg/h.). These findings explained the lower Cp value recorded in birds pretreated with toltrazuril which is similar to the value recorded previously in chickens for Diclazuril & doxycycline (0.37, El-Gendi *et al.,* 2010).

The Vdss of thiamphenicol in control broilers was found to be (2.31 L/kg) which was lower significantly than those determined in broiler chickens pretreated with toltrazuril (Vdss, 3.51L/kg) . Those findings showed that the thiamphenicol concentration in birds pretreated with toltrazuril was lower with wide distribution. However, this result was significantly higher than Vdss recorded for TP in turkeys (0.83 L/kg, Switała *et al.,* 2007) , FF in ducks (0.58L/kg) and TP in ducks (0.68 L/kg) (Tikhomirov *et al.,* 2019) and TP in quail (0.84 L/kg, Aboubakr and Soliman, 2020).

Following oral administration, the obtained data revealed that the serum concentrations of thiamphenicol were significantly reduced at different time intervals in broiler chickens pretreated with toltrazuril compared to those in control group. The decreased levels of thiamphenicol may be explained by the slower absorption of thiamphenicol from the gut of chickens which may be attributed to negative interaction with toltrazuril.

Thiamphenicol serum concentration was significantly lesser in toltrazuril pretreated broilers. The apparent absorption rate in chickens pretreated with toltrazuril is significantly increased (0,38± 0,103 h–1) compared to normal chickens (0.34 h-1). Moreover, the absorption half-life was decreased significantly (1.81±0.01h) in broilers formerly taken toltrazuril relative to normal chickens (2.06±0.01h).

In control broilers, the calculated values of C_{max} and T_{max} (14.58 µg.ml^{-1} and 3.64 h, respectively) described in current study were agreed with those values formerly reported for florfenicol in rabbit (15.14µg/ml, Abd El-Aty *et al.,* 2004). On the other hand, the obtained values were greater than those described formerly for TP in turkeys (8.99 µg/ml, 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).

The calculated C_{max} for thiamphenicol in birds pretreated with toltrazuril (C_{max} 11.88 µg.ml-1) was lower than control ones (Cmax 14.58 µg.ml-1 µg.ml-1). These finding were similar to those reported for FF and anthelmintics in goats (Atef *et al.,* 2010**).** Based on the impact of toltrazuril on the microsomal hepatic enzymes, the lower Cmax of thiamphenicol in broilers pretreated with toltrazuril can be clarified.

In control broilers, the elimination half-life was (T0.5el, 2.65h) which was similar to the values reported for FF in broiler chickens (2.25 hr , Shen *et al.,*2003), FF in rabbit (2.35hr, Park *et al.,* 2007) and ducks (2.77 hr, Tikhomirov *et al.,* 2019). but much shorter than values recorded previously for FF in Muscovy ducks (7.41hr, El-Banna, 1998) and TP in turkeys (7.40 hr, Kowalski, 2007), TP in ducks (3.27 hr , Tikhomirov *et al.,* 2019), TP in quails (4.01 hr, Aboubakr & Soliman 2020). On the other hand, these values were longer than those documented for FF in dog (1.24 h, Park *et al.,* 2008) in birds pretreated with toltrazuril the elimination half-life of thiamphenicol was (T0.5el, 2.87h). The

reported value for the biological half-life of thiamphenicol suggesting that birds pretreated with toltrazuril can slowly remove the drug compared to control chickens.

These results agreed with that of Atef *et al.* (2020) who concluded that *Eimeria* infected birds pre-treated with toltrazuril can eliminate enrofloxacin more slowly compared to control chickens. This difference can be due to the effect of toltrazuril on the removal of drug.

The elimination rate constant in birds pretreated with toltrazuril was (kel, 0.24 h-1) compared with control ones (kel, 0.26h-1).

Following oral administration, the findings recorded indicated lower systemic bioavailability of F % of thiamphenicol in birds pretreated with toltrazuril (F %, 114.85 ±0.7) relative to control birds (F %, 117.79 ± 1.2). Close similarity was also documented for Thiamphenicol in pig (112.9%, Liu *et al.,* 2003), FF in broiler chickens (94%, Shen *et al.,* 2003) and FF in dog (95.43%, Park *et al.,* 2008). Moreover, this values was higher than those recorded for thiamphenicol in turkeys (68.24 %, Switała *et al.,* 2007), TP in quails (78.10%, Aboubakr and Soliman 2020), FF in ducks (73.86% , Tikhomirov *et al.,* 2019), but, this values was less than that of TP in chickens (138.58% , Chen & Pu 2008). The lower systemic bioavailability F % of thiamphenicol in birds pretreated with toltrazuril (F%, 114.85 ±0.7) than in control birds is agreed with (El-Banna *et al.,* 2013) who concluded that toltrazuril resulted in a significance decrease in oral bioavailability which found to be 107.47 ± 9.23 in control group and 53.51 ± 2.45% in toltrazuril pretreated group.

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