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PHARMACOKINETICES AND TISSUE RESIDUES OF TETRACYCLINE IN CHICKENS FOLLOWING ORAL ADMINISTRATION

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ABSTRACT

Tetracyclines are one of the antibiotics classes that have been extensively used in poultry farms in therapeutic doses for treatment and prevention of bacterial infections and in sub-therapeutic doses for growth promotion. This may result in the presence of their residues in edible tissues intended for human consumption, causing a health threat. Therefore, this study was conducted to obtain the pharmacokinetics parameters of tetracycline in broiler chickens and tissue residues. The pharmacokinetics profile was studied after oral administration at dose of 70mg/kg bodyweight. Plasma concentrations were determined using modified microbiological assay method. The inhibition zones diameters were interpreted with tetracycline standard curve to determine plasma and tissue concentrations. A peak level of tetracycline C_{max} 41.30±6.20 mg/µl was achieved after t_{max} of 0.9±0.15h and half-life (t½ β) was 11.51±3.86h and the volume of distribution Vd was found to be 0.48±0.13L/kg. the total clearance (Cl β) was 0.93±0.16µl^{-1} and the mean resident time was 10.43±4.83. A total of 150 tissue samples (Liver, kidney, muscle) was screened for detection of residues after multiple doses of 70 mg/kg body weight of tetracycline administered orally for 5 days. Tissue samples were collected at 1, 3, 7, 10 and 12 days after drug administration. The samples were processed using microbiological assay method. The highest concentrations were detected 1286.76

±375.13µg/g, 848.265±135.082 and 9341.62±420.51 in liver, kidney and muscle respectively at day 1 while day 12 showed significant lower concentrations of tetracycline above maximum residue limits (MRL).

INTRODUCTION

Tetracycline which was prescribed extensively to the poultry farms as a microbial agent (Gigvere, 2006, Greenlees, Fried Lander and Boxall; 2011), feed conversion and to make the production system profitable (sarker, 2016, Gelbad *et al*., 2015). Moreover, Gross contaminated Feed and water contaminated with Metal, pesticides, toxic chemicals were accumulated in liver, kidney, muscle and bones (Nouws *et al*., 1993) exceeding the maximum residual limits (MRL) which were mentioned by WHO (WHO, 2010)and FAO, and this lead to several pathological implications which may pose serious public health hazards.

To ensure human safety (Alaboudi, 2013) international Organization have a set tolerance or maximum residue limits (MRLS) for parent compound of tetracycline in muscle at level of 200µg/kg, 600µg/kg in liver and 1200µg/kg in kidney.

The pharmacokinetics of tetracycline are reviewed indifferent animal species such as sheep (Ziv and Sulmanm 1974, Wilson, 1980), goats (Escudero *et al*, 1966), chickens (Anodan, 1985, dogs (Baggot *et al*., 1977), Cow (Meijer *et al*., 1993). Due to polar nature and high aqueous solubility (Zakeri, 2008) and (David, 2006) tetracycline are highly absorbed after oral administration from gastrointestinal tract and spread in body (Doyle, 2006, Mund *et al*., 2017). Thus the metabolism of tetracycline are known to bind to plasma protein at varying degrees in different species of animal and have a short half-life and low toxicity (Mol, H.,1975) (Nielsen, 1996 and Davis, 2006).

The aim of this study is to evaluate the pharmacokinetics of tetracycline and to investigate the presence of antibiotic residues in broiler tissues after therapeutic treatment.

MATERIAL AND METHODS

Pharmacokinetics profiles study

Fifteen healthy broiler chickens, weighing between 1.0-1.3kg and aged 35-40 days were used. They were housed and maintained in suitable cages. The feed and water was available *ad libitum*. Therapeutic dose of tetracycline (TETRA, 100 soluble powder Barcelona, Spain)

was given orally at dose of (70mg/kg) according to manufacturer's approved. Blood samples (1.5-2µl) were collected from each chicken from wing vein in sterile heparinized tube before and after drug administration at time O(pre-treatment). 15^{min}, 30^{min}, 1 h, 2, 4, 6, 9, 12, 18 and 24h after dosing. The plasma was collected by centrifugation of the blood and Frozen at -20^{o}C until analysis.

Detection of tetracycline residues

Fifty healthy broiler chickens of 35-40 days age and 1-1.3 kg weight were used. The chickens were maintained at a suitable condition. A therapeutic dose of tetracycline was administered orally in drinking water for 5 successive days. The chickens were slaughtered at the end of the experiment and tissue sample (liver, kidney and muscle) were collected in sterile plastic container at 1, 3, 5, 10, 12 days after the last administration and frozen at 0^{o}C for drug assay.

Microbiological assay

The concentration of tetracycline in both plasma and tissue samples were detected microbiologically by using *Bacillus subtilis* BGA (DSM618) as a test organism. The method was modified by (Koenen-Dierick *et al*., 1998).

Standard curve of the drug was obtained from the diameters of inhibition zones of the microorganism and the concentration of standard tetracycline prepared in pooled plasma. The logarithm concentrations of tetracycline of known concentrations were plotted versus mean inhibition zones diameters from the standard curve the concentrations of test samples were estimated.

Statistical analysis

The obtained data were performed using soft were Microcal origin 8, 2002(USA) and SPSS program using ANOVA with significance difference $P<0.05$).

RESULT

The mean plasma concentrations of 70 mg/kg bodyweight to 15 boiler chickens following oral administration were represented in table (1) and figure.

Table 1: Mean± SEM of tetracycline concentrations following oral administration of 70 mg/kg body weight to boiler chickens (n=15).

Time (Hours)	Drug concentrations (µg/ml)
0	0
15(min)	28.5±0.1
30(min)	34.1±0.8
1	38.2±0.01
2	41.60±0.802
4	37.00±0.1
6	33.5±0.2
9	29.8±0.11
12	23.9±0.312
18	16.02±0.18
24	7.0±0.01

Different pharmacokinetic parameters were summarized in table (2)

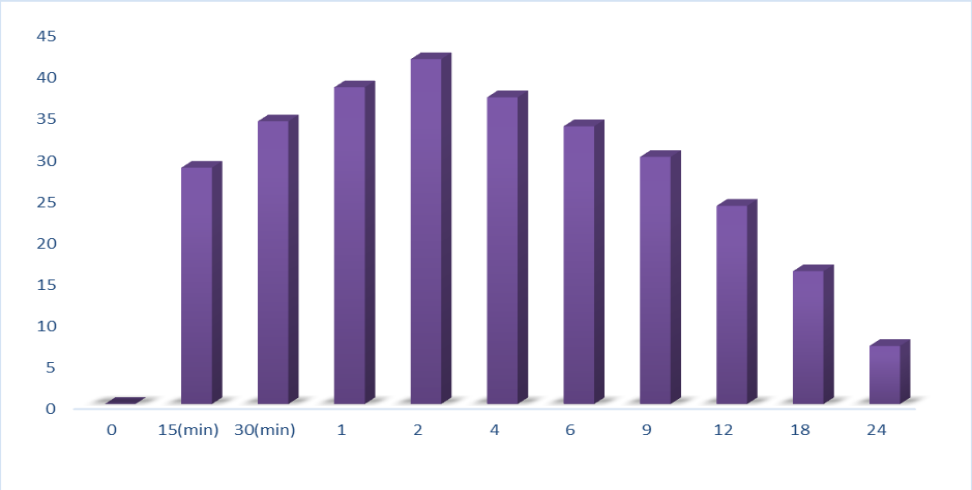

Figure 1: Mean± SEM of tetracycline concentrations following oral administration of 70 mg/kg body weight to boiler chickens (n=15).

Table 2: Mean±SEM of pharmacokinetic parameters of tetracycline after single oral administration (70 µg/kg body weight) to 15 broiler chickens.

Pharmacokinetics parameters	Values (mean±SEM)
A (µg/kg/ml $^{-1)}$	106.3±0.26
B (h^{-1})	1.91±0.21
Kel (h^{-1})	0.1262±0.013
K_{12} (h^{-1})	0.130±0.083
K_{24} (h^{-1})	0.0123±0.004
C_{max} (µg $µl^{-1}$)	41.30±6.201
T_{max} (h)	0.93±0.15
$T_{½}$ A(h)	6.3±405
$T_{½}$ B(h)	7.51±3.86
Vd (area)(L)	0.48±0.13

Au^{o}C24(µg µl/h)	2982.23±14.063
Au^{o}C α (µg µl/h)	2791.20±0.053
Aum ^{o}Cα (µg µl/h)	3192.65±341.01
MRT (h)	10.43±4.831
Cl (ml/h)	0.63±0.16

The disposition kinetics of tetracycline revealed that the maximum peak plasma concentrations C_{max} were 41.30±6.20 (µg/µl and attained at t_{max} of 0.9±.15 hours and was eliminated with half –life $t_{½}$ B of 11.51±3.86 hours. The volume of distribution was found to be 0.48±0.13L while the total body clearance cl (µl/h) was calculated as 0.63 ±0.16 (µl/h).

The area under the maximum curve was determined as 3192.65±34.1.01 (µg µl/h) but the mean resident time was found to be 10.43 ±4.83 h.

The examined tissue samples of broiler chickens which administered reported doses of tetracycline for 5 days showed different concentrations of the drug table 3.

Table 3: Mean± SEM of tissue concentration of tetracycline following oral administration of 70/ µg/kg for five consecutive days in broiler chickens (n=50).

Day/ tissue	Day 1	Day 3	Day 5	Day 10	Day 12
Liver	1286.76±375.13	986.84±.261	384.02±237.14	173.20±105.16	68.01±102
Kidney	848.265±.135.082	768.0224±452.07	737.97±235.05	618.20±201.31	25.4±22.04
Muscle	934.62±420.51	798.12±321.03	672.78±81.16	270.33±0.49	142.17±.019

Highly concentration were observed 1286.76 ±375.13µg/g in liver , 848.265±135.082 in kidney and 9341.62±420.51 in muscle at day 1 and significantly decreased gradually until reached the lowest levels in day 12.

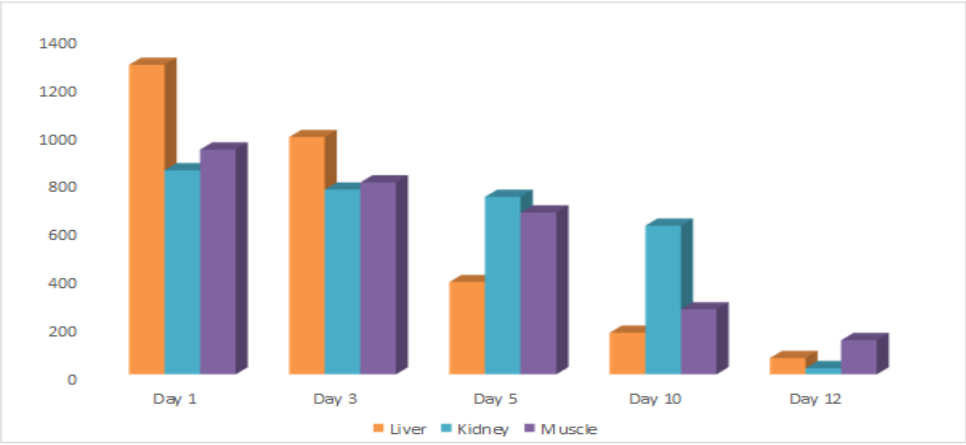

Figure 2: Mean± SEM of tissue concentration of tetracycline following oral administration of 70/ µg/kg for five consecutive days in broiler chickens (n=50).

DISCUSSION

The pharmacokinetic of tetracycline, administered orally 15 broiler chickens were compatible with the two-compartment open model, which was mentioned for chickens by Andan, 1985. Therefore, distribution and elimination were found to be best described (Baggot, 1977). Plasma concentration of tetracycline reached a maximum level C_{max} 41.30±6.20 (µg/ µl^{-1}**)** after t_{max} 0.93±0, 15 (h). These findings are nearly similar with those reported by

And less than that obtained by (Riveiere, 2009). The higher C values and AUC were suggesting highly absorption and distribution of the drug. The apparent volume of distribution were nearly similar to that obtained by Kniffen (1989) in pigs (4.5L.kg) and Rajaian (2006) in sheep (3.37L). These highest values could be due to higher dilution of the drug, resulting to widely distribution and good penetration into tissue and fluids. (Shargel 2005). These was accompanied with prolongation of half life which were relatively increasing with the holding time of the drug (Riviere, 2009). Our finding were less than those reported in Rabbits (1-1oL/kg) Percy, 1988, Anadon, 1985 (0.2L) in chickens cow and ewes (3.3L/kg) Ziv and Sulman, 1974 and Laczay (2001) in chickens (1.4L/kg) achieved after intravenous administration the difference could be due to the difference in dosage and different species of animal. As shown in table (2) the elimination half-life $t_{½}$ of tetracycline in chickens was with the range of these reported by Ziv and Sulman, 1975 in cows and ewes (5.7) hr, Escudero, *et al*., 1994 in goat (6.5 hr) and Laczay *et al*., (2001) in chickens (6.8hr) but higher than that obtained after intravenous injections in Rabbit (2.0hr) Percy, 1989) and Pig (2.8hr) Kniffen *et al*., 1989. The difference could be attributed to different route of administrations.

The total body clearance of tetracycline was nearly close to that recorded in chicken (0.54 µl –min $^{-1}$ kg^{-1}) by Tell *et al*., 2003 following intravenous route and lower than that achieved in chickens (1.6 µl/min/kg) Andon, 1985, Rabbit (6.1 µl/min/kg) Percy (1988) and Turkeys (3.7 µl/min/kg) Dyer (1989).

The observed values of MRT (10.43±4.8hr^{-1}) was agree with that of (ZiolkowskiH, 2015) in chickens (10.37±391h) following oral administration the highly positive detectable levels of tetracycline concentrations in plasma and tissue indicated a wide spread distribution in liver, muscle and kidney. These result are consistent with many previous studies which have reported the presence of antibiotic residues in examined poultry tissue samples. Ezenduka *et al*., 2014), Morshdy (2015) and Elnasri *et al*., (2014) whom found that the occurrence of

antibiotic residue in chickens (Liver, muscle and kidney) were higher than (MRL) maximum residues limits (MRLs) reported by FAO (1995).

Highest concentrations were found in liver and kidney, muscle in the first day of sacrifice and persisted longer up to 12 days. The concentrations decreased gradually until reached the minimum levels on day 12 similar observations were achieved in hens by (Serrano *et al.*, 1999), chickens (Salama *et al*., 2011), and (Shalaby 2011) who using Hplc as a test method.

In this study the highest detected levels of tetracycline concentrations in liver and kidney explained that the liver is the main target organ for metabolism and detoxification of the drug while the kidney is the excretory organ for the elimination. Our finding confirmed by different studies (Oh *et al*., 2006), (Alwar, 2013) and (Tse Ramtla, 2017).

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