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Pharmacology

Kinetic Disposition of Lincomycin After Oral Administration in Broiler Chickens

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ABSTRACT

The kinetic disposition of lincomycin in broiler chickens was studied after single oral administrations at a dose of 10 mg /kg b.wt. Serum concentrations of lincomycin were determined by using reverse phase HPLC. Following compartmental analysis, a two-compartment open model best described the concentration-time data of lincomycin after oral administration. After oral administration, the drug reached its maximum serum concentrations (C_{max}) of 5.892 ± 0.060 µg/ml at maximum time (T_{max}) of 1.241 ± 0.015 h, absorption half-life ($t_{1/2ab}$) and (AUC_{0-t}) were 0.347 ± 0.016 h and 48.868 ± 0.175 µg/ml.h respecrtively. Lincomycin was eliminated at a rate (K_{10}) equal to 0.147 ± 0.006 h and cleared by all clearance processes (Cl/F) in the body at rate of 0.312 ± 0.004 (mg/kg)/(µg/ml)/h. In conclusion, lincomycin administered orally at dose of 10 mg/kg b.wt showed a good pharmacokinetic profile with a long elimination half-life ($t_{1/2\beta}$) 7.041 ± 0.402 h.

Keywords: *Lincomycin , Kinetic , HPLC , broiler chickens.*

INTRODUCTION

Lincomycin is a lincosamide antibiotic closely related to macrolide. It inhibits protein synthesis through binding to the 50S bacterial ribosome subunit. It is mainly active against Gram-positive bacteria, obligate anaerobes and against mycoplasmas. Lincomycin distributes well into tissues and is known to produce high intracellular concentrations. It is used alone or in combination with other drugs like spectinomycin in poultry for oral treatment of
bacterial enteric infections, control of respiratory infections and growth promoters. The pharmacokinetic profile of lincomycin has been previously studied in pigs (Chaleva E. and Nguyen D.L., 1987; Nielsen P. and Gyrd-Hansen N., 1998; Hui Min F. et al., 2012), broiler chickens (Soback S. et al., 1987; El-Sayed M.G. et al., 2015), goat (Abo El-Soud K. et al., 2004; Sharma et al., 2017; Sharma M. and Dumka V.K., 2018; Saganuwan S.A. et al., 2019; Sharma et al., 2019), cats (Albarellos G.A. et al., 2011; 2013), buffalo calves (Gouri S.S. et al., 2014), sheep (Ziv G. and Sulman G., 1973) and dogs (Brown R.B. et al., 1975). The objective of this study was to describe the pharmacokinetic profile of lincomycin after oral administrations to broiler chickens.

MATERIAL AND METHODS

1- Materials

Drug

Lincomycin Hcl (Lincoprima®, primavet, Cairo, Egypt) water soluble powder is supplied for oral solution in strength: lincomycin hcl 468 mg (equivalent to 400 mg lincomycin base) per gram.

Chickens

Our study was used seven apparently healthy broiler chickens of 2.0 ± 0.5 kg. All chickens were obtained from poultry breeding farm. All chickens were housed separately in cages and were fed on balanced drug free ration for two weeks to ensure complete excretion of any drugs from their bodies. Water was supplied *ad-libitum*. Chickens were reared in room maintained at 12 h lighting cycle with constant temperature and relative humidity of 45% to 65%.

Experimental design

Chickens were weighted separately before drug administration and doses were calculated precisely for each bird. Seven chickens were given a single oral dose of lincomycin at 10 mg/kg b.wt.

Blood samples (1 ml) were collected after oral administration from brachial and cutaneous ulnar veins at time 0, 5, 10, 15, 30 min and 1, 2, 4, 8, 10, 12, 24 hours after oral administration. The samples were left to clot at room temperature then centrifuged at 3500 rpm for 10 minutes and serum was stored frozen at -20 ºC until analyzed for lincomycin.

2-Methods

Determination of lincomycin in serum: Lincomycin was extracted according to (Nielsen and Gyrd-Hansen, 1998) as following: 1.25 ml acetonotrile were added to 1.0 ml of serum then shaked for 15 sec. Centrifugation for 10 min at 4600 x g at room temperature. Remove the upper layer and 1.5 ml of the aqueous layer was transferred in to a new tube then 2 ml of ethyl acetate was added upon which the samples were shaken for another 30 sec followed by centrifugation at 4600 x g at room temperature. The upper layer was transferred to another tube and evaporated to dryness at 37°C. The residue was dissolved in 300 µl of HPLC-eluent by shaking for1 min, filtered and the filtrate transferred into the auto-sampler vial for analysis.

Lincomycin concentration was determined by reverse phase HPLC according to (Nielsen and Gyrd-Hansen, 1998). The mobile phase consists of phosphate buffer: acetonitrile (75:25) which always freshly prepared, filtered and degassed. The injection volume of samples was 50 µl and the flow rate was fixed at 1.0 ml/min, at room temperature with ultra violet detector wavelength at 210 nm.

Preparation of standard curve of lincomycin in serum:

Standard concentrations of lincomycin were prepared in antibacterial free chicken's serum and deionized water. Lincomycin hydrochloride (purity ≥ 95.0%) was purchased from Sigma aldrich (3050 Spruce Street, Saint Louis, MO 63103, USA). The standard curves for serum, and deionized water were linear between 0.50 and 100 µg/ml. A calibration curve was obtained by plotting lincomycin peak areas versus known concentrations. The equation was calculated by the least-squares method using linear regression. The assay was sensitive, reproducible and linearity was observed from 0.50 to 100 µg/ml. The retention time of lincomycin was 1.724 min.

Pharmacokinetic analysis:

The pharmacokinetic parameters were calculated by PKSolver: An add-in program for Microsoft Excel, version 2. The data were calculated as mean ± standard deviation according to (**Berly and Lindgren 1990**).

RESULTS:

Serum lincomycin disposition after oral administration:

Following oral administration of lincomycin, the serum concentration-time data was best fitted to two compartments open model. Lincomycin was detected in serum in a therapeutic level for 24 hours with mean value 0.445 ± 0.037 µg/ml (**Figure 1**). The pharmacokinetic parameters following a single oral administration of lincomycin were recorded in (**Table 1**). The obtained results revealed that absorption half-life ($t_{1/2ab}$) was 0.347 ± 0.016 h while the absorption rate constant (K_{ab}) was 2.004 ± 0.091 h^{-1}. Lincomycin reached its maximum concentrations (C_{max}) 5.892 ± 0.060 µg/ml after maximum time equal to (T_{max}) 1.241 ± 0.015 h. it was slowly

eliminated with half-life ($t_{1/2\beta}$) was 7.041 ± 0.402 h. Lincomycin was cleared by all clearance processes (Cl/F) in the body at rate of 0.312 ± 0.004 µg/ml/h. The area under serum concentration time curve of lincomycin after a single oral administration (AUC_{0-t}) was 48.868 ± 0.175 µg/ml.h.

Fig. (1) Mean ± SD serum concentration (µg/ml) of lincomycin in broiler chickens after single oral administration of 10 mg/kg b.wt.

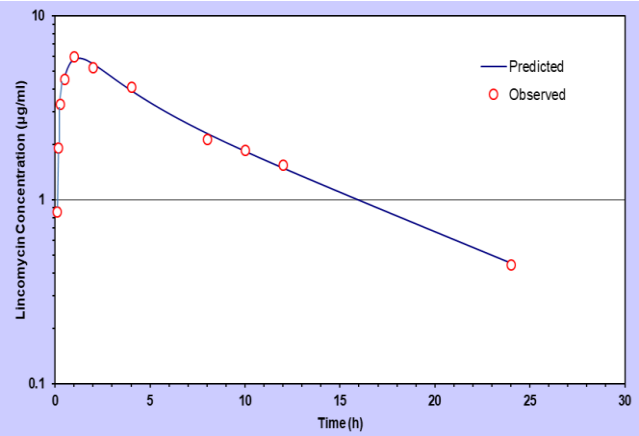

Table (1) Mean ± SD pharmacokinetics parameters of lincomycin after single oral administration of 10 mg/kg b.wt. (n=7).

Parameters	Units	Mean ± SD
A	µg/ml	4.254 ± 0.465
α	h^{-1}	0.455 ± 0.072
T_{max}	h	1.241 ± 0.015
C_{max}	µg/ml	5.892 ± 0.060
K_{ab}	h^{-1}	2.004 ± 0.091
$t_{1/2\alpha}$	h	1.557 ± 0.242
$t_{1/2\beta}$	h	7.041 ± 0.402
CL/F	$\mu g/ml.h^{-1}$	0.312 ± 0.004
$t_{1/2ab}$	H	0.347 ± 0.016
AUC_{0-t}	µg/ml.h	48.868 ± 0.175
AUMC	µg/ml.h2	511.30 ± 24.517
MRT	H	9.566 ± 0.341

A, zero-time intercept of the distribution slope; **α**, distribution rate constant; **$t_{1/2\alpha}$**, the distribution half-life; **$t_{1/2\beta}$**, elimination of drug was reached after extra vascular administration (h); **C_{max}**, Maximum serum concentration of drug in blood after extravascular administration (µg/ml); **Cl**, total body clearance; **AUC_{0-t}**, area under the [serum drug concentration versus time] curve; **k_{ab}**, absorption rate constant.

DISCUSSION

In this study, the drug disposition after oral administration of (10 mg/kg b.wt.) in chickens was best fitted by a two-compartment open model which agreed with that reported in broiler chickens following i.v administration (El-Sayed M.G. et al., 2015) and in chickens after i.m administration (Soback S. et al., 1987).

Following a single oral administration, lincomycin was rapidly and efficiently absorbed in chickens with half-life ($t_{1/2ab}$) was (0.347 ± 0.016 h). Lincomycin reached to a maximum serum concentration (T_{max}) after (1.241 ± 0.015 h) which nearly similar to lincomycin that previously reported in broiler chickens (1.16 ± 0.02 h, El-Sayed M.G. et al., 2015), but disagreed with those reported in goats (0.53 ± 0.21 h; 0.20 ± 0.16 h, Abo El-Sooud K. et al., 2004; Sharma et al., 2017) after intramuscular administration respectively and in broiler chickens after intramuscular administration (0.25 ± 0 h, Soback S. et al., 1987). The mean peak serum concentration of lincomycin (C_{max}) was (5.892 ± 0.060 µg/ml) which nearly similar to that previously discussed in broiler chickens (7.08 ± 0.16 µg/ml; 4.01 ± 0.30 µg/ml, El-Sayed M.G. et al., 2015; Soback S. et al., 1987) after oral and intramuscular administration respectively, in cats after intramuscular administration (7.97 ± 2.31 µg/ml, Albarellos G.A. et al., 2011), in goats after intramuscular administration (5.28 ± 0.64 µg/ml; 5.63 ± 2.50 µg/ml, Abo El-Sooud K. et al., 2004; Sharma et al., 2017) respectively, and in pigs (5.10 ± 3.6 µg/ml; 5.15 ± 0.18 µg/ml, Nielsen P. and Gyrd-Hansen N., 1998; Hui Min F. et al., 2012) after oral and intramuscular administration respectively. Variation in species as well as doses could be considered the causes of these variations.

The AUC reported in this study was (53.429 ± 0.652 µg/ml.h) which higher than that

half-life; T_{max}, The time at which the maximum concentration

reported in broiler chickens (31.49 ± 1.103, El-Sayed M.G. et al., 2015), in goats after intramuscular injection (9.30 ± 1.31; 10.8 ± 7.68, Abo El-Sooud K. et al., 2004; Sharma et al., 2017) but lower than that discussed in broiler chickens after intramuscular administration (314 ± 23, Soback S. et al., 1987).These differences in AUC is probably because of the differences in doses, species as well as route of administration.

In conclusion, lincomycin administered orally at dose of 10 mg/kg b.wt showed a good pharmacokinetic profile with a long elimination half-life ($t_{1/2\beta}$) 7.041 ± 0.402 h.

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