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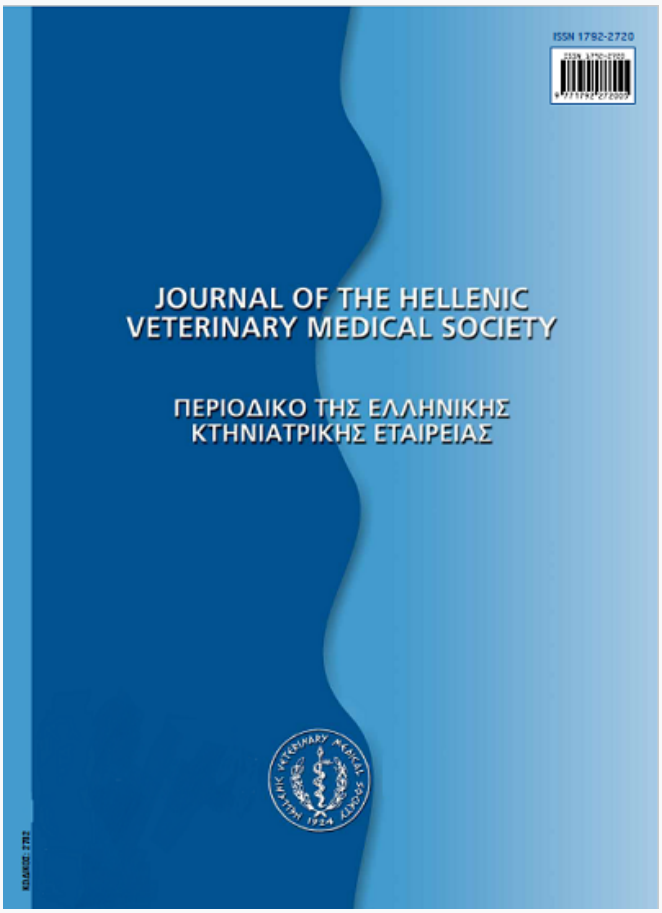

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Original article
Ερευνητικό άρθρο

Comparative pharmacokinetics and bioavailability of two tylosin formulations in chickens after oral administration

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Συγκριτική φαρμακοκινητική και βιοδιαθεσιμότητα δύο σκευασμάτων τυλοσίνης σε κοτόπουλα μετά την από του στόματος χορήγηση

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Abstract

The pharmacokinetics and oral bioavailability of two tylosin formulations was carried out in broiler chickens according to a single dose, randomized, parallel design. The two formulations of tylosin (Tylosina® and Tylan®) were given orally at a dose level of 25 mg/kg b.w. after an overnight fasting (n=15 chicken/group). To calculate tylosin bioavailability, fifteen more chickens was assigned as group 3 and was given a single intravenous dose of tylosin (25 mg/kg b.w.). Serial blood samples were collected at different time points up to 24 hour post-drug administration. A high performance liquid chromatography (HPLC) method was used for the determination of tylosin concentrations in chicken plasma. The pharmacokinetics analysis of the data was performed using non-compartmental analysis based on statistical moment theory with the help of commercially available software (WinNonlin®, Pharsight Corporation, Cary, NC, USA). There were no significant differences in the C_{max} (3.05±0.63, 2.63±0.74 μg/ml), t_{max} (2.36±0.42, 2.30±0.38 h), $t_{1/2\beta}$ (1.99±0.38, 2.67±0.60 h), AUC_{0-12h} (6.11±0.97, 5.37±1.16 μg.h/ml), $AUC_{0-\infty}$ (6.38±0.94, 5.57±1.15 μg.h/ml), MRT (3.53±0.24, 3.67±0.32 h), Cl_B/F (90.59±13.81, 169.38±54.44 ml/min/kg) and Vd_z/F (16.85±4.74, 43.96±18.24 l/kg) between Tylosina® and Tylan®, respectively. The calculated oral bioavailability (F) for Tylosina® and Tylan® were 40.56 and 35.41%, respectively. Moreover, the relative bioavailability of

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Tylosina® was 113.9% when compared to Tylan®. In conclusion, Tylosina® is comparable to Tylan® and both formulations can be used for treatment of susceptible microorganisms in veterinary medicine practice at a dose level of 25 mg/kg b.w.

Keywords: tylsoin, pharmacokinetics, bioavailability, chicken.

Περίληψη

Η φαρμακοκινητική και βιοδιαθεσιμότητα δύο σκευασμάτων τυλοσίνης χορηγούμενων από το στόμα πραγματοποιήθηκε σε κοτόπουλα κρεατοπαραγωγής με την μέθοδο απλής δόσης, τυχαιοποιημένου και παράλληλου σχεδιασμού. Τα δύο σκευάσματα της τυλοσίνης (Tylosina® και Tylan®) χορηγήθηκαν από το στόμα σε δόση 25 mg/kg σ.β. μετά από νηστεία μιας βραδιάς (n=15 κοτόπουλα/ομάδα). Για τον υπολογισμό της βιοδιαθεσιμότητας της τυλοσίνης, δεκαπέντε επιπλέον κοτόπουλα ορίστηκαν ως ομάδα 3 και τους χορηγήθηκε μια απλή ενδοφλέβια δόση τυλοσίνης 25 mg/kg σ.β. Δείγματα αίματος συλλέχθηκαν σε διάφορους χρόνους μέχρι και 24 ώρες μετά τη χορήγηση του φαρμάκου. Η μέθοδος της υγροχρωματογραφίας υψηλής απόδοσης (HPLC) χρησιμοποιήθηκε για τον προσδιορισμό των συγκεντρώσεων της τυλοσίνης στο πλάσμα. Η φαρμακοκινητική ανάλυση των δεδομένων πραγματοποιήθηκε χρησιμοποιώντας την ανάλυση του μη διαμερισματικού προτύπου με τη στατιστική θεωρεία στιγμής και τη βοήθεια εμπορικά διαθέσιμου υπολογιστικού προγράμματος (WinNonlin®, Pharsight Corporation, Cary, NC, USA). Δεν υπήρχαν σημαντικές διαφορές στην τιμή C_{max} (3.05±0.63, 2.63±0.74 μg/ml), t_{max} (2.36±0.42, 2.30±0.38 h), $t_{1/2\beta}$ (1.99±0.38, 2.67±0.60 h), AUC_{0-12h} (6.11±0.97, 5.37±1.16 μg.h/ml), $AUC_{0-\infty}$ (6.38±0.94, 5.57±1.15 μg.h/ml), MRT (3.53±0.24, 3.67±0.32 h), Cl_B/F (90.59±13.81, 169.38±54.44 ml/min/kg) και Vd_z/F (16.85±4.74, 43.96±18.24 l/kg) μεταξύ των σκευασμάτων Tylosina® και Tylan®, αντίστοιχα. Η υπολογισμένη βιοδιαθεσιμότητα (F) από το στόμα ήταν 40,56 και 35,41%, αντίστοιχα. Επιπλέον, η σχετική βιοδιαθεσιμότητα του Tylosina® ήταν 113,9% σε σχέση με το Tylan®. Συμπερασματικά, το σκεύασμα Tylosina® είναι συγκρίσιμο με το σκεύασμα Tylan® και αμφότερα τα σκευάσματα μπορούν να χρησιμοποιηθούν για την αντιμετώπιση ευαίσθητων μικροοργανισμών στην κτηνιατρική πράξη σε δόση 25 mg/kg σ.β.

Λέξεις ευρετηρίασης: τυλοσίνη, φαρμακοκινητική, βιοδιαθεσιμότητα, κοτόπουλο

INTRODUCTION

Tylosin is a macrolide antibiotic, registered exclusively for veterinary use and was first described by Stark et al. (1961). Tylosin is active against Gram-positive bacteria, anaerobic bacteria and mycoplasmas (Giguere 2006). It is indicated primarily for the treatment of chronic respiratory disease complex caused by *Mycoplasma gallisepticum* and *synoviae* in chickens and infectious sinusitis in turkeys (Montesissa et al. 1999 , Kowalski et al. 2002). On the other hand, it is prescribed extensively for the treatment of bovine and swine respiratory infections (Taha et al. 1999, Prats et al. 2002, Saurit et al. 2002). Tylosin is considered as a bacteriostatic time-dependent antibacterial agent that inhibits bacterial protein synthesis through blocking the translocation step (Burrows 1980, McKellar et al. 2004, Giguere 2006).

Mycoplasmas are of considerable veterinary importance, causing infections of the respiratory and urogenital tracts, mammary glands, joints and eyes of poultry and livestock species (Hannan et al. 1997, Jordan et al. 1998, David 2003, Loria et al. 2003). Tylosin is still considered as one of the most effective antimicrobial agents against different mycoplasmas species and has more activity against mycoplasma than bacteria (Burrows 1980, Atef et al. 1991, Kowalski et al. 2002).

Several pharmacokinetic studies have been reported for tylosin in cows and buffalo (Gingerich et al. 1977, Saurit et al. 2002), camels (Ziv et al. 1995), pigs (Prats et al. 2002), sheep and goats (Atef et al. 1991, Taha et al. 1999) and dogs (Weisel et al. 1977). Despite the extensive use of tylosin in poultry industry, limited information is currently available about pharmacokinetic disposition of tylosin in broiler chickens (Kowalski et al. 2002). Accordingly, the aim of the present study was to determine the pharmacokinetics and oral bioavailability of two tylosin formulations. The results of the present study may contribute to the further understand tylosin plasma disposition kinetics in broiler chickens.

MATERIALS AND METHODS

Drugs

Tylosina® 20% liquid solution (NeoFarma, Italy) and Tylan® 100% water soluble powder (Elanco, USA) were used for oral administration. Tylosin standard (Tylosin tartate, 90 %, Sigma-Aldrich, St Louis,

USA) was used for intravenous injection. The drug was dissolved in water for injection to give a final concentration of 200 mg/ml prior administration.

Experimental animals

Forty five broiler chickens (Hubbard x Hubbard) of 35-40 days old, weighing from 1.7 - 2.0kg were used in this study. The chickens were purchased from local poultry farm. They were placed in the animal house at Jordan University of Science and Technology (JUST). The animals were monitored for 2 weeks for any apparent clinical signs of disease before drug administration. The animal house temperature was maintained at 25 ± 2°C and humidity at 45–65%. The chickens had free access to water and antibacterial-free food (consisted of maize, soybean, and premix) ad libitum daily.

Experimental design

The chickens were allotted into 3 groups. Chickens of group 1 and 2 (n= 15/group) were given a single oral dose of Tylosina® and Tylan® at a dose level of 25 mg/kg b.w. The dose was chosen according to the manufacturers' instruction. Chickens were weighed prior drug administration and the doses were calculated accordingly. Tylosin was given directly into the crop using a thin plastic tube attached to a syringe. Chickens of group 3 (n=15) was given a single intravenous dose of standard tylosin powder (25 mg/kg b.w.) in the right brachial vein. Food was withheld for 12 h before drug administration and was offered 6 h after drug administration. The study followed a randomized parallel design. All procedures were approved by the animal care and use committee, Faculty of Veterinary Medicine, JUST.

Sample collection

Blood samples (1-1.5 ml) were collected from the left brachial vein and cutaneous ulnar veins into heparinized tubes at 0 (pre-treatment), 10, 20, 30, 45 min, and at 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 h after oral administration. After intravenous administration, blood samples were collected at 0, 5, 15, 30 and 45 min and 1, 2, 4, 6, 8, 10, 12, 24 h. The samples were centrifuged directly at 1000x g for 5 min and then the plasma was harvested and stored at -20 °C and analyzed within 72 h after collection.

Analytical method and sample preparation

The High Performance Liquid Chromatography (HPLC) method has been modified from previously described method (Abu-Basha et al. 2007, Juhel-Gaugain et al. 1999). Briefly, frozen plasma samples were thawed at room temperature and 200 µl plasma were taken to Eppendorf tube and precipitated with 200 µl perchloric acid (8%) (Sigma-Aldrich, St Louis, MO, USA). Each sample was shaken with vortex mixer for 30 seconds and then centrifuged for 5 min at 1500x g. The clear supernatant was transferred into glass insert, fitted into auto-sampler vial and 100 µl was injected into the HPLC system (*Shimadzu, Japan*).

The chromatographic separation was performed using a purospher Star RP-18e (5 µm, 125 mm × 4.6 mm) column (Merck, Germany) with an isocratic mobile phase of acetonitril: water (30: 70) (HPLC-grade Scharlau Chemie S.A., Barcelona, Spain) and 0.5% of triflouroacetic acid (Sigma-Aldrich, St Louis, MO, USA) was added to the mobile phase. The mobile phase was filtered through a 0.45 µm membrane filter (Millipore, Billerica, MA, USA) and degassed. The mobile phase was eluted at flow rate of 1.5 ml/min and detected at UV wavelength of 287 nm.

Calibration curve and validation procedure

A standard calibration curve was prepared by adding 20 µl of tylosin (1 mg/ml) to 980 µl antibacterial-free chicken plasma. This was further diluted into antibacterial-free chicken plasma to produce standard of 0.025, 0.05, 0.1, 1, 5, 10, 25 and 50 µg/ml. Standard solutions were extracted and analyzed in the same manner as unknown samples. Calibration curves were obtained by calculating the area of tylosin and plotting them against the corresponding concentration of tylosin spiked in chicken plasma by integration peak program (Class-vp *Shimadzu, Japan*).

The HPLC method was validated by assessing linearity, precision, recovery and sensitivity. Two standard calibration curves with 8 concentrations (0.025, 0.05, 0.1, 1, 5, 10, 25 and 50 µg/ml) and 6 sets of quality control samples (0.25, 2.5 and 7.5 µg/ml) were prepared and analyzed three times daily for 3 consecutive days. The calibration curves were linear over the range of 0.025-50 µg/ml (r2>0.9996). The calculated limit of detection (LOD) and the limit of quantification (LOQ) were 0.025 and 0.05 µg/ml based on a signal-to-noise ratio of 3:1 and 6:1, respectively.

The mean analytical recovery percentage of tylosin in plasma was ranged from 92.6 to 98.4%. The inter- and intra-day assay coefficients of variation ranged from 1.54 to 6.75% at concentrations of 0.25, 2.5 and 7.5 μg/ml. The accuracy ranged from 97.8- 100.2%.

Pharmacokinetic and statistical analysis

The pharmacokinetic analysis of the data was performed using non-compartmental method based on statistical moment theory (SMT) according to previously described method (Gibaldi and Perrier 1982), using the commercially available software (Win Nonlin®, Pharsight Corporation, Cary, NC, USA). The calculated parameters were: area under plasma concentration-time curve (AUC) and the area under the moment curve (AUMC) using linear trapezoid method; mean residence time (MRT), where MRT= AUMC/AUC; volume of distribution (Vd_z/F), where Vd_z/F = dose/AUC.β; elimination rate constant (k_{el}), which is the slope of the terminal log-linear portion of the plasma concentration-time profile, determined by least squares regression; AUC and AUMC extrapolated to infinity, by adding the ratio $Clast/k_{el}$; elimination half-life ($t_{1/2\beta}$), where $t_{1/2\beta} = 0.639/ k_{el}$; total body clearance (Cl_B/F), where Cl_B/F = dose/AUC; The maximum concentration (C_{max}) and the corresponding peak time (t_{max}) were determined by the inspection of the individual drug plasma concentration-time profiles. Relative bioavailability was calculated as ($AUC_{Tylosina}$® /AUC_{Tylan}®) x 100%. The absolute bioavailability (F) was calculated as (AUC_{non-IV} /AUC_{IV}) x 100%.

Differences between the pharmacokinetic parameters of the two tested formulations were evaluated by one-way analysis of variance (ANOVA) using the commercially available software package (SPSS Inc., version 10.0, Chicago, IL, USA). Data were expressed as mean ± SE. The differences were considered significant when $P<0.05$.

RESULTS

All chickens used in the present study were clinically healthy throughout the experimental period and both products were well tolerated. Unexpected incidents that could have influenced the outcome of the study did not occur. The mean plasma concentration was 35.45±1.93 μg/ml at 5 min following intravenous administration of tylosin (25 mg/kg b.w.). The plasma concentration was sharply decreased to reach the detection limit (0.05±0.01 μg/ml) at 12 h post-injection.

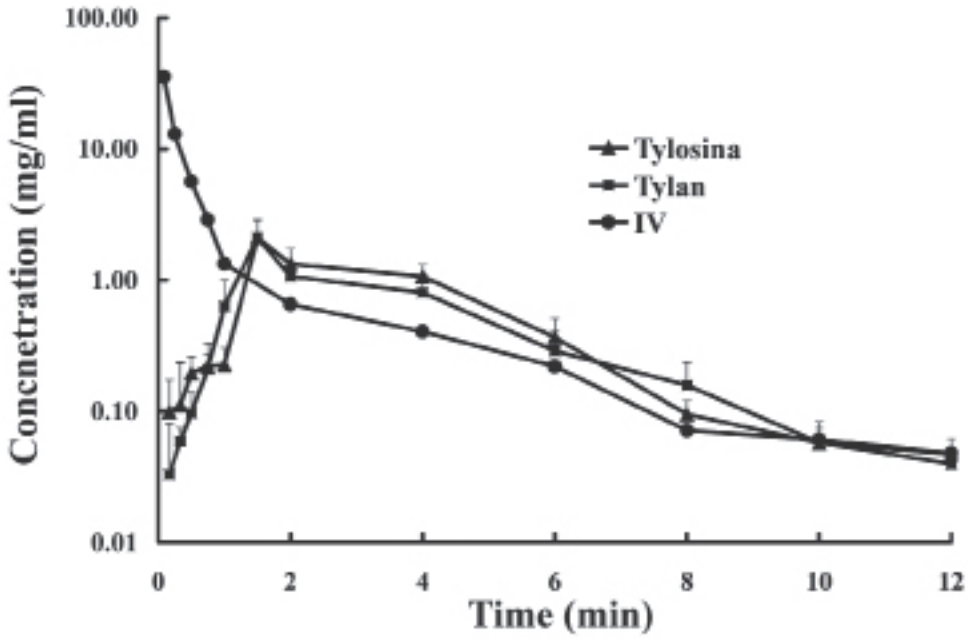

Figure 1. Semilogarthimic plot, showing the mean plasma concentrations–time profile of tylosin in chickens after a single intravenous and oral administration at a dose level of 25 mg/kg b.w. Values are mean ± SE (n=15/group).

Table 1. Comparison of the mean plasma pharmacokinetic parameters obtained for tylosin in chickens after a single intravenous and oral administration at a dose level of 25 mg/kg b.w. Values are mean ± SE (n=15/ group).

Parameters	Units	IV	Oral Formulations	
			Tylosina®	Tylan®
C_{max}	µg/ml	-	3.05±0.63	2.63±0.74
t_{max}	h	-	2.36±0.42	2.30±0.38
$t_{1/2\beta}$	h	2.06±0.30	1.99±0.38	2.67±0.60
AUC_{0-12h}	µg.h/ml	15.62±1.50	6.11±0.97	5.37±1.16
$AUC_{0-\infty}$	µg.h/ml	15.73±1.50	6.38±0.94	5.57±1.15
MRT	h	0.91±0.25	3.53±0.24	3.67±0.32
Cl_B/F	ml/min/kg	28.29±2.86	90.59±13.81	169.38±54.44
Vd_z/F	l/kg	4.87±0.58	16.85±4.74	43.96±18.24
F	%	-	40.56	35.41

C_{max}, maximum plasma concentration; t_{max}, time to peak concentration; $t_{1/2\beta}$, elimination half-life; AUC_{0-12h}, area under plasma concentration-time curve from zero to 12 h post drug administration; $AUC_{0-\infty}$, area under plasma concentration-time curve from zero to infinity; MRT, mean residence time; F, systemic bioavailability; Cl_B/F, total body clearance/F; Vd_z/F, volume of distribution/F.

The mean concentrations–time profile for tylosin after intravenous administration is shown in Figure 1.

The concentrations of tylosin in chicken plasma were determined up to 12 h and were below the detectable limit in all chickens 24 h post single oral administration for both formulations. Both formulations were slowly absorbed after oral dosing with a peak plasma concentration (C_{max}) of 3.05±0.63 and 2.63±0.74 µg/ml, achieved at (t_{max}) 2.36±0.42 and 2.30±0.38 h, respectively for Tylosina® and Tylan®. The mean concentration–time profile for tylosin oral products is shown in Figure 1.

The oral bioavailability (F) for Tylosina® and Tylan® were 40.56 and 35.41%, respectively and the relative bioavailability was 113.9 % (Tylosina®/ Tylan®). The pharmacokinetics parameters after intravenous and oral administrations of the two formulations are shown in Table 1.

DISCUSSION

Tylosin is an organic base with high lipid solubility that achieves good tissue and barrier penetration, readily entering the peripheral compartment and allowing the drug to accumulate at therapeutic levels at the targeted site of infection (Atef et al. 1991, Giguere 2006). Tylosin is widely distributed in the body, which attains higher concentration at the tissue compared to that at the plasma and has low binding to plasma proteins (Burrows 1980, Taha et al. 1999, Brennan et al. 2001). Tylosin is concentrated in tissues including

lungs at levels between 3 to 5 times greater than those detected in plasma (Kowalski et al. 2002, Giguere 2006). Despite the extensive use of tylosin in poultry industry, limited information is currently available about the mathematical disposition of tylosin in broiler chicken. Lack of data about the pharmacokinetic of tylosin in chickens and other avian species obligate the authors to refer to other species such as sheep, goat and pigs for pharmacokinetics comparison.

After a single intravenous administration of tylosin (25 mg/kg b.w.), the elimination half-life ($t_{1/2\beta}$) expresses the overall rate of drug elimination and can be used to predict drug accumulation in the body. The mean value of $t_{1/2\beta}$ (2.06 ± 0.30 h) was longer than those reported in broiler chickens (0.52 ± 0.02 h) (Kowalski et al. 2002). This dissimilarity may be attributable to differences in the administered dose (10 versus 25 mg/kg b.w.). However, this value was shorter than those reported in sheep and goat (4.75 ± 0.71 and 4.24 ± 0.32 h, respectively) (Taha et al. 1999) and in pigs (4.52 h) (Prats et al. 2002).

The clearance obtained in the present study (28.29±2.86 ml/min/kg) was higher than those reported in chickens (5.30±0.59 ml/min/kg) (Kowalski et al. 2002) and in sheep and goat (6.89±0.94 and 8.66±1.37 ml/min/kg, respectively) (Taha et al. 1999) and was similar to those reported in pigs (26.8 ml/min/kg) (Prats et al. 2002). On the other hand, the apparent volume of distribution (V_{dz}) provides an estimate of the extent of drug distribution in the body in which drugs with V_{dz}> 1 l/kg imply a wide distribution (Riviere 2009). The V_{dz} value of 4.87±0.58 l/kg indicates extensive drug distribution in the chickens' body. This value is higher than those previously reported for broiler chicken (0.69±0.03 l/kg) (Kowalski et al. 2002). However, our data was close to those reported in sheep and goat (3.12 ± 0.34 and 2.74 ± 0.56 l/kg, respectively) (Taha et al. 1999) and in pigs (1.4 l/kg) (Prats et al. 2002).

Following oral administration of Tylosina® and Tylan®, both formulations were slowly absorbed with a maximum plasma concentrations (C_{max}) of 3.05±0.63 and 2.63±0.74 μg/ml achieved at t_{max} of 2.36±0.42 and 2.30±0.38 h , respectively. The observed C_{max} values were higher than those reported in chickens at a dose level of 10 mg/kg b.w. (1.2±0.2 μg/ml) (Kowalski et al., 2002). The difference in C_{max} (2.2-2.5 x) is expected since the administered dosage in our study is 2.5 x higher. On the other hand, the reported t_{max} in this experiment was 2.36±0.42 and 2.30±0.38 h for Tylosina® and Tylan®, respectively. These values were longer than those reported in broiler chickens (1.5±0.3 h) (Kowalski *et al.* 2002). The oral bioavailability (F) for tylosin represented by Tylosina® (40.56%) and Tylan® (35.41 %) was slightly higher than those reported in broiler chickens (30 %) (Kowalski et al. 2002). The differences in the AUC may be attributed to the differences in the achieved bioavailability.

On the other hand, the average means of AUC_{0-12}, $AUC_{0-\infty}$, C_{max} for The two oral formulations were not significantly different, indicating that the plasma profiles produced by Tylosina® are comparable to those produced by Tylan®. Moreover, no significant differences were found among all tested pharmacokinetic parameters including; elimination half-life ($t_{1/2\beta}$), mean residence time (MRT), total body clearance (Cl_B/F) and volume of distribution (Vd_z/F).

Tylosin is a macrolide antibiotic with a minimum inhibitory concentration (MIC) values ranging from 0.01 to 0.5 μg/ml for various susceptible bacterial and mycoplasmal pathogens (Jordan and Horrocks 1996, Hannan et al. 1997, Jordan et al. 1998, Salmon and Watts 2000). Tylosin (Tylosina® and Tylan®) was detected in chicken plasma at concentrations higher than the MIC for most susceptible microorganisms and Mycoplasma for 12 h following oral administration. Therefore, oral tylosin administration at a dose of 25 mg/kg b.w. seems to be a suitable therapeutic dose in broiler chickens. However, repeated doses are necessary to maintain tylosin plasma concentrations above the MIC for most susceptible microorganisms.

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