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Original Research Article

Pharmacokinetic interaction of tulathromycin with Flunixin meglumine after intravenous injection in goats

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ABSTRACT

The pharmacokinetic aspects of tulathromycin (2.5 mg/kg b.w.) were studied following intravenous administration alone and in combination with flunixin meglumine (2.2 mg/kg b.w) in apparently healthy goats. Tulathromycin concentrations in serum were determined by microbiological assay technique using *Bacillus subtiles* (ATCC 66343) as test organism. The half-lives of distribution and elimination ($t_{0.5}(_a)$and to.5(p)) were 0.071, 0.046 and 6.43, and 5.05 h. following intravenous injection of tulathromycin alone and in combination with flunixin, respectively. Volume of distribution at steady state (Vdss) was 0.249 and 0.96l/kg., mean residence time (MRT) was 6.27 and 5.99 h and total body clearance (Cl_B) was 0.046 and 0.17 l/kg/hr., respectively. It was concluded that flunixin significantly altered the pharmacokinetics of tulathromycin by increase its distribution and accelerate its elimination from body. Therefore care should be taken during use of tulathromycin in goats concurrently with flunixin.

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1. **Introduction**

Tulathromycin is a novel triamilide antimicrobial in the macrolide class shown to be safe and effective in cattle and swine to treat bacterial respiratory disease (**Benchaoui et al., 2004; Nowakowski et al., 2004; Evans, 2005**). Macrolide structure facilitates rapid distribution of these drugs from the blood stream into tissues (**Williams &Sefton, 1993**). Newer macrolides, such as azithromycin and tulathromycin, have increased lung tissue uptake and longer half-lives than older macrolides such as erythromycin (**Benchaoui et al., 2004**). In addition, the tripleionized form of tulathromycin produces displacement of the Mg^{2+} ions present in the outer cell wall of gram-negative bacterial pathogens, facilitating drug entry into these agents (**Evans, 2005**). As a macrolide, tulathromycin exerts its activity through binding to the 50S subunit of bacterial ribosomes and blocking peptidyltransferase which results in dissociation of transfer RNA (tRNA), cessation of peptide translocation, and blockage of protein synthesis (**Benchaoui et al., 2004; Evans, 2005; Villarino et al., 2013**). Although this drug is classified as bacteriostatic, it can also exhibit bactericidal activity at higher concentrations (**Benchaoui et al., 2004; Evans, 2005; Nowakowski et al., 2004; Villarino et al., 2013**). **Brunton et al. (2008)** recorded that in addition to impacting enhanced tissue and cellular penetration characteristic of all macrolides, this novel structure (tulathromycin) conveys desirable antibacterial properties particularly against Gram negative respiratory bacteria. Tulathromycin is more efficacious injectable macrolide antibiotic used for the treatment of pneumonia of ruminants compared with other antibiotics in recent years **(Venner** *etal.,* **2007; Nutsch** *et al.,* **2005; Godinho** *et al.,* **2005; Skogerboe** *etal.,* **2005 and Robb** *et al.,* **2007).**

Non steroidal anti-inflammatory drugs (NSAIDs) are inhibitors of cyclooxygenase that catalyze the incorporation of molecular oxygen into arachidonic acid to produce prostanoids (eg, thromboxanes, prostacyclin, and prostaglandin) and are effectively administered for inflammation and pain. Flunixin is one of (NSAIDs) has been reported to reduce fevers and improve clinical signs of endotoxemia (**Anderson et al., 1986**). Flunixin has been widely used for their anti-inflammatory and analgesic prosperities to treat the musculoskeletal conditions and colic in equine. It was also used routinely in ruminant practice to treat mastitis, endotoxemia and pneumonia **(Zu-Gong et al., 2007).** It is well documented that concurrent administration of drugs together may alter the pharmacokinetic parameters of these drugs. In veterinary practice the administration of antibiotics and NSAIDs at the same time was more common. Therefore, the aim of the study was to compare the disposition kinetic of tulathromycin in goats after a single

intravenous administration alone and when administrated with flunixin meglumine.

Material and Methods

Drugs: Tulathromycin 100 mg ml^{-1} was supplied as an injectable solution (Draxxin®) by animal health division Pfizer Company, Cairo, Egypt. Flunixinmeglumine (Flunidyne) is a product of ArabcoMed, Egypt.

Animals: Ten apparently healthy, male and female Egyptian goats (3-9 months old and mean body weight of (12-23 kg) were used. Animals were obtained from a local market at Beni-Suef province, kept under good hygienic condition, fed barseem and free access to water.

Methods:

Experimental design: The animals were randomly divided into two groups (five goats each). Animals of first group were injected intravenously with tulathromycin in alone single dose of2.5 mg kg^{-1} **(Clothier et al., 2011, Young et al., 2011; Grismer et al., 2014)**. While the 2^{nd} group was intravenously injected with a single dose of tulathromycin and 2.2 mg kg^{-1}flunixin (**Konigssonet al., 2003**) in the right jugular vein. Blood samples were collected viavein puncture from left jugular vein before and 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours post-administration. Blood samples were left to clot then centrifuged at 3000 revolution per minute for 15 minutes to obtain clear serum that was kept frozen at -20 °C until assayed.

Drug bioassay

Samples were assayed by microbiological assay according to the method of **Arret et al. (1971)** using *Bacillus subtiles* (ATCC 6633) as a test organism. Standard tulathromycin concentrations of 0.078, 0.156, 0.3125, 0.625, 1.25, 2.5, 5, 10 and 20 ug ml^{-1}were prepared in antibiotic- free goat serum and phosphate buffer saline (pH 8). The minimal detectable limit for the assay method was 0.078ugml^{-1}. Semi-logarithmic plots of the inhibition zone diameter versus standard tulathromycin concentrations in serum and phosphate buffer were linear with typical correlation coefficient of 0.992 (for the standard curve).

Pharmacokinetic analysis:

A computerized curve stripping program (R Strip; Micromath Scientific Software, Salt Lake City, UT, USA) was used to analyze the serum concentration-time curves for each individual animal using the statistical moment theory **(Gibaldi and Perrier, 1982)**. Following IV injection, the serum concentration-time relationship was best estimated as a two-compartment open model system **(Baggot, 1978),**according to the following bi-exponential equation: $C_p = Ae^{-at} + Be^{-at}$, where C_p is the

concentration of drug in the serum at time t; A is the intercept of the distribution phase with the concentration axis expressed as ug ml^{-1}; B is the intercept of the elimination phase with the concentration axis expressed as ug ml^{-1}; a is the distribution rate constant expressed in units of reciprocal time (h^{-1}); p is the elimination rate constant expressed in units of reciprocal time (h^{-1}); and e is the natural logarithm base. Results were expressed asmean and standard error (S.E). Standard errors were calculated from the mean data according to **Snedecorand Cochran (1976)**.

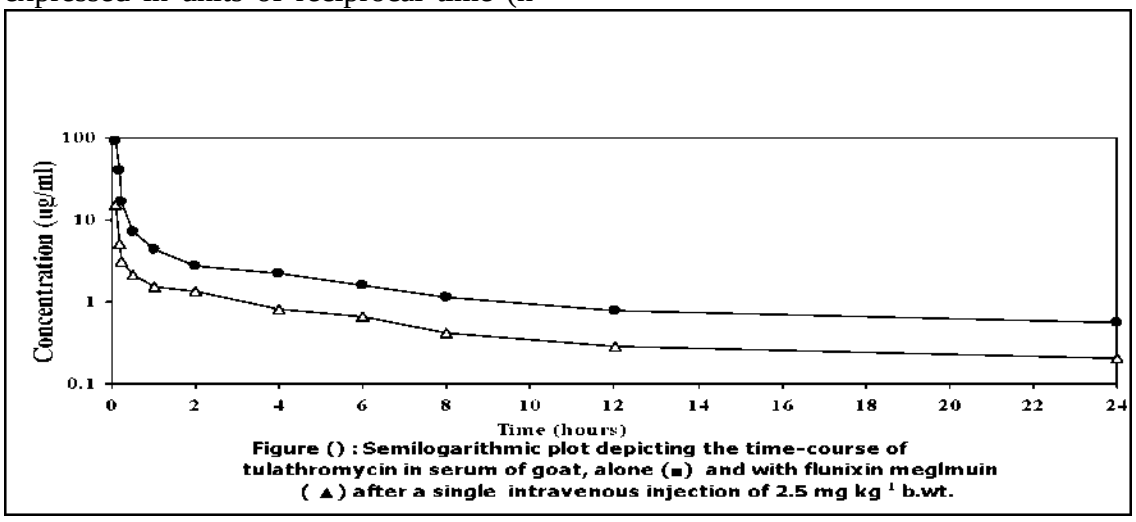

Figure (1): Semi-logarithmic graph depicting the time-concentration of tulathromycin in serum of goats after a single intravenous injection of 2.5 mg kg^{-1}b.wt alone (■) and with flunixin (A).

Results:

Disposition of tulathromycin in serum after intravenous injection was best fitted by the 2-compartment open pharmacokinetic model (Figure 1). The pharmacokinetic parameters of tulathromycin following a single intravenous administration of 2.5 mg kg^{-1}b.wt alone and with flunixin are recorded in table (1). The results of the present study revealed that tulathromycin was rapidly distributed following intravenous injection when administrated with flunixin where the distrubtionhalf lives were ($t_{0.5(a)}$) 0.071 when given alone and 0.046 h with flunixin. The body clearance (Cl_B) was 0.46 and 0.17 l/kg.h, the volume of distribution at steady-state (Vd_{ss}) was 0.249 and 0.96 L/kg, respectively.

Table (1): Pharmacokinetic parameters of tulathromycin alone (of 2.5 mg kg^{-1}b.wt) and with flunixin (of 2.2 mg kg^{-1}b.wt) following a single intravenous injection in goats (n=5). (Mean ± SE)

Pharmacokinetic parameter	tulathromycinalone	Tulthromycin with flunixin
Cp° (ug/h)	257.3±77.01	72.3±35.4*
A (ug/ml)	252.8±76.5	70.3±35.1*
a (h^{-1})	11.17±2.05	16.7±2.74
$t_{0.5a}$ (min)	0.071±0.013	0.046±0.007
B (ug/ml)	4.51±0.6	2.0±0.36**
P (h^{-1})	0.14±0.028	0.18±0.032
$t_{0.5\,P}$ (h)	6.43±2.13	5.05±1.64
K_{12} (h^{-1})	6.34±0.84	11.78±0.61***
K_{21}(h^{-1})	0.35±0.048	0.79± 0.12
K_{el}(k_{10}) (h^{-1})	4.62±1.23	4.3±1.67**
V_c (l/kg)	0.0132±0.003	0.061±0.015**
Vd_{ss} (l/kg)	0.249±0.076	0.96±0.29**
CL_B (l/kg/hr)	0.046±0.054	0.17±0.015***
AUC (ug.h.ml^{-1})	57.1±7.11	15.45±1.48***
AUMC (gg.h^{2}.ml^{-1})	78.97±6.3	24.71±1.95***
MRT (h)	6.27±2.57	5.99±2.29

Cp° concentration at zero time (immediately after single IV injection); A, B zero-time intercepts of the biphasic disposition curve; a, P hybrid rate constants representing the slopes of distribution and elimination phases, respectively; k12 first-order constant for transfer from central to peripheral compartment; k_{21}firstorder constant for transfer from peripheral to central compartment; K_{el}elimination rate constant; t0.5(a) distribution half-life; t0.5(P) elimination half-life; MRT mean residence time; AUCarea under serum concentration-time curve; AUMC area under moment curve; $V_c$apparent volume of the central compartment; Vd_{ss} volume of distribution at steady state; Cl_B total body clearance. (*** P ≤ 0.001 ,**P ≤ 0.01, *P ≤ 0.05)

Discussion:

In veterinary medicine, antimicrobial and anti-inflammatory agents are commonly co-administered for management of pain and treatment of various infections.Following alone intravenous injection of tulathromycin in a single dose of 2.5 mg/ kgb.wt.in goats, the serum concentration time curve was best fitted by a two -compartment open model. Our result was disagreed with most of the results reported for tulathromycin in pigs **(Benchaoui et al., 2004; Wange et al., 2012)** rabbits **(Abo-El-Sooud et al., 2012)** and calves **(Tohamy et al., 2011).** The difference in kinetic parameters are relatively common and are frequently related to interspecies variation, age, breed, health status of the animals and/or the assay method used **(Haddad et al., 1985)**.In the interaction study theresults were consistent with that reported for the effect of flunixin on other antimicrobials as with sulphadimidine in horses by**El-Banna(1999),**enrofloxacin in rabbits **(Elmas et al., 2008)** andwith the finding reported by **(Tohamy, 2011**) for orbifloxacin and flunixin in buffalo calves. But, differ from the findings recorded by (**El-Hewaity, 2014**) for flunixin and enrofloxacin in goats.

The drugwhen administrated with flunixinwas rapidly distributed with a distribution half life $t_0.5(_a)$ of 0.046 h and it was slightly lower than when tulathromycin given alone (0.071 h) this was agreed with (**Tohamy et al., 2011)**

(0.13) h for orbifloxacin and flunixin. The rapid distribution of tulathromycin when administered concurrently with flunixin is indicated by the low value of p (0.18 h) than that of *a* (16.76h) due to increased tissue distribution this is in accordance with that recorded by **Iqbal et al.(2009**) and**Tohamy(2011**)**.** Volume of distribution at steady state ($Vd_{(ss)}$ = average of 0.96 L /kg) was in accordance with that reported by (**Tohamy, 2011**) for orbifloxacin and flunixin in buffalo calves (1.04 L/kg) and that observed by (**El-Hewaity, 2014**) (0.47 L/kg) for cefepime and flunixin in goats , this increase of Vd(ss) over Vc indicated that the peripheral compartment is the major compartment for tulathromycin distribution at steady state.

Tulathromycin with flunxin was relatively rapidly eliminated with an elimination half life of $to._5$(p) of 5.05 h.(this result was higher than that when administratedalone (6.43 h) this findings were in accordance with that reported by (**Tohamy, 2011**) (4.95 h) for orbifloxacin and flunixin in buffalo calves, and (**El-Banna, 1999**) for sulphadimidine in horses. This rapid of elimination of the drug from the body is coincident with high rate of clearance (CL_B=0.17 L/ kg/ h), this result was agreed with that reported by **Tohamy(2011**) (0.15 L/kg/h) for orbifloxacin and flunixin in buffalo calves and that observed by **El-Hewaity (2014**) for cefepime in goats with flunixin (0.096 L/ kg/ h). The observed decrease in drug clearances as a result of co-administration of flunixin indicates that these drugs interact during the elimination phase (**Ongio et al., 2005**).Tulathromycin was distributed when combined with flunixin in the central compartment with a volume of distribution (V_c =average of 0.061 L /kg), this was lower than that of (**Whittem et al., 1996)** for ciprofloxacin with flunixin in human (59.22 L /kg), (0.262 L /kg) for penicillin G with phenylebutazone (**Firth et al., 1990**) and for enrofloxacon with flunixin in rabbits (4.98 L/kg) (**Iqbal et al., 2009**). It was concluded that, the combination of flunixin with tulathromycin altered the kinetics of tulathromycin after intravenous injection in healthy goats.

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