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Original Research Article

Subcutaneous pharmacokinetic interaction of tulathromycin With flunixin meglumine in goats

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ABSTRACT

The pharmacokinetic aspects of tulathromycin(2.5 mg/kg) administered alone and in combination with flunixin meglumine (2.2 mg/kg) after a single subcutaneous (SC) administration, werestudied in clinically healthy goats. The animals were divided into two groups: the 1st group was given tulathromycin alone and the 2nd group was given tulathromycin concurrently with flunixin meglumine. Serum concentrations of tulathromycin were determined using microbiological assay method. Tulathromycin was rapidly absorbed with a half-life of absorption ($t_{(0.5)ab}$) of 0.54 h and the peak plasma concentration (C_{max}) was 3.7ug/ml was attained after 0.98 h (T_{max}). Flunixin significantly altered the pharmacokinetics of tulathromycin by increasing its absorption and delay its elimination from body where $t_{0.5(ab)}$were 0.54 and0.34 h and the elimination half-lives ($t_{0.5(el)}$) were 1.35 and 1.8 h, for alone and combination groups, respectively. Significant decreases (39.8%) in the area under the curve (AUC) and (22.6%) in the elimination rate constant (Kel) from the central compartment were found following coadministration with flunixin compared with administration of tulathromycin alone. It was concluded that the combination of tulathromycin and flunixin negatively altered the kinetics of tulathromycin.

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1. **Introduction**

Macrolide antibiotics are antibacterial agents used as veterinary drugs in food-producing animals with either a curative or prophylactic aim (Codony et al., 2002). It active against Gram-positive bacteria, they target the bacterial ribosome and inhibit bacterial protein biosynthesis (Leal et al., 2001). Triamilides are semisynthetic derivatives of the natural product, erythromycin, and are characterized bythe presence of three polar aminegroups (tribasic) that differentiate themstructurally from other macrolides (Letavic et al., 2002). Tulathromycin is the first member of a new macrolide class, the triamilides, developed exclusively forveterinary use (Evans, 2005).Newer macrolides, such as tulathromycin, have been designed with modified configurations to enhance invitro and in vivo antibacterial properties along with increasing bioavailability, lung tissue penetration, and extended tissue half-lives (Benchaoui, et «/.,2004; Retsemea& Fu, 2001).

Tulathromycin demonstrates better tissue penetration and longerhalf-lives than older macrolides due to its lipophilic properties (Benchaoui eta/., 2004; Evans, 2005). This activity can provide unique therapeutic advantage in treating bacterial respiratory infections in livestock species. 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 eta/., 2007; Nutsch et a/., 2005; Godinho et a/., 2005; Skogerboe eta/., 2005 and Robb et a/., 2007). Tulathromycin injectable solution is effective as a means of mass treatment to prevent bovine respiratory disease (BRD) and reduce the number of retreats and chronics in stocker calves (Richeson, 2008 and Nutsch, 2005). Tulathromycin is used for treatmentand prevention of BRD associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis. Also, It is used for treatment of infectious bovine keratoconjunctivitis (IBK) associated with Moraxella bovi (CVMP, 2002).

Flunixinis non steroidal anti-inflammatory drug (NSAID) inhibiting cycloxygenase enzymes in the arachidonic acid cascade, thus block the formation of cycloxygenase derived eicosanoid inflammatory mediators (Landoni et al., 1995; Cheng et al., 1998). Flunixin is widely used in veterinary medicine, to treat the musculoskeletal conditions, endotoxic shock, acute mastitis, endotoxemia, and calf pneumonia (Anderson et al., 1991; Welsh & Nolan, 1995; Odensvik& Magnusson, 1996; Rantala et al., 2002). Due to its anti-inflammatory, analgesic, and antipyretic effects (Mckellar et al., 1989; Beretta et al., 2005).Consequently,

the present study describes some pharmacokinetics aspects of tulathromycin after single subcutaneous administration in goats. Also, to assess the effect of co-administration of flunixin on pharmacokinetic behavior of tulathromycin.

Material and Methods

Drugs: Tulathromycin 100 mg ml-1 was supplied as an injectable solution (Draxxin®) by animal health division Pfizer Company, Cairo, Egypt. Flunixin meglumine (Flunidyne) is a product of ArabcoMed, Egypt. Animals: Ten apparently healthy, male and female Egyptian goats (3-9 months old and mean body weightof (12-23 kg) were used. Animals were obtained from a local market at Beni-Suef governorate kept under good hygienic condition and fed barseem free access to water.

Methods:

Experimental design: the animals were randomly divided into two group's five goats each. Animals of first group administered a single dose of 2.5 mg kg-1tulathromycin subcutaneously (Clothier et al., 2011, Young et al., 2011; Grismer et al., 2014), while the 2nd was injected2.5 mg kg-1tulathromycin with 2.2 mg kg-1flunixin subcutaneously (Konigssonet al., 2003). Blood samples were collected via vein puncture from 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-1were 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). The difference of inhibition zone diameter between the solutions of the drug in serum and buffer was used to calculate the in-vitro protein binding tendency of tulathromycin according to Craig and Suh (1991) by the following equation:

Protein binding % = Zone of inhibition inbuffer-Zone of inhibition in serum x 100

Zone of inhibition in buffer

Pharmacokinetic analysis:

A computerized curve strippingprogram (R Strip; Micromath Scientific Software, Salt Lake City, UT, USA) was used toanalyze the concentration-time curves for each individual animal using the statistical moment theory (Gibaldi and Perrier, 1982). Following SC administration, The Cmax (maximum serum concentration) and tmax (time of maximum serum concentration) were taken directly from the curve. The

terminal elimination half-life (t0.5(ei)) and absorption half-life (t0.5(ab)) were calculated as ln2/Kel or ln2/Kab, respectively, where Kel and Kab are the elimination and absorption rate constants, respectively. The area under serum concentration-time curve (AUC) and area under the first moment curve (AUMC) were calculated by the method of trapezoids and extrapolation to infinitywas performed. Results were expressed asmean and standard error (S.E). Standard errors werecalculated from the mean data according to Snedecorand Cochran (1976).

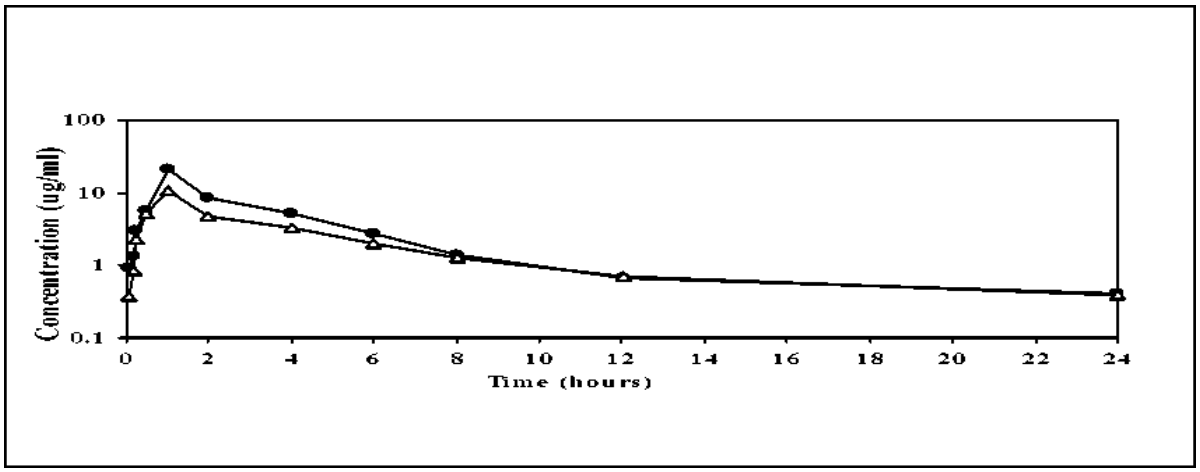

Figure (1): Semi-logarithmic graph depicting the time-concentration of tulathromycin in serum of goats after a single subcutaneous injection of 2.5 mg kg^{-1}b.wt alone (■) and with flunixin (A).

Results:

Disposition of tulathromycin in serum after subcutaneous injection was best fitted by the 2-compartment open pharmacokinetic model (Figure 1).The pharmacokinetic parameters of tulathromycin following a single subcutaneous 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 absorbed following a single subcutaneous injection alone and with flunixin with $t_{o.5(ab)}$ of 0.54 and0.34 h and maximum serum concentrations (C_{max}) of3.7 and 2.59ug ml^{-1} were achieved at (t_{max}) of0.98 and 0.95 h., respectively. The elimination halflives ($t_{0.5(el)}$) were1.35 and 1.8 h. for tulathromycin alone and with flunixin, respectively. The *in-vitro* serum protein-binding tendency was calculated to be 18.72%.

Table (1): Pharmacokinetic parameters of tulathromycin alone (2.5 mg kg^{-1}b.wt) and with flunixin (2.2 mg kg^{-1}b.wt) following a single subcutaneous (SC) administration in

goats (n=5). (Mean ± S.E)

parameters	Alone	With flunixin
K(ab) (h^{-1})	1.53±0.079	2.1±0.25*
$^{t}0.5ab$ (h)	0.54±0.066	0.34±0.03*
Kel (h^{-1})	0.53±0.049	0.41±0.056
$^{t}0.5$ el (h)	1.35±0.125	1.8±0.24
^{t}max (h)	0.98±0.09	0.95±0.089
Cmax (ug/ml)	3.7±1.09	2.59±0.43
AUC (pg.h.ml)	50.14±4.75	30.7±3.95***
AUMC ($pg.h^2.ml^{-1}$)	73.17±4.74	52.55±7.11*
MRT (h)	2.62±0.17	3.1±0.35
MAT (h)	0.66±0.036	0.5±0.049*
IBD (h)	87.7±10.8	79.5±6.97

k_{ab} first-order absorption rate constant; K_{el} elimination rate constant; Cmax maximum serum concentration; t_{max} time to peak serum concentration; $t_{0.5(ab)}$ absorption half-life; $t_{0.5(el)}$ elimination halflife; MAT mean absorption time; F fraction of drug absorbed systemicallyafter SC injection; MRT mean residence time; AUCarea under serumconcentration-time curve; AUMC area under moment curve; IBD interval between doses. (*** P < 0.001 ,** P < 0.01, * P < 0.05)

Discussion:

Pharmacokinetic interactions between NSAIDs and antimicrobial drugs have received little attention in veterinary medicine, in spite of their frequent use in combination. However, pharmacokinetic interactions between phenylbutazone and the antibiotics benzyl-penicillin and gentamicin have been studied in horses (**Whittem et al., 1996**). Phenylbutazone increased the serum concentrations of penicillin in one study but there was no effect of phenylbutazone on gentamicin pharmacokinetics. Flunixin meglumine found to have no effect on either orbifloxacin pharmacokinetics in buffalo calves (**Tohamy, 2011**) or cefepime in goats (**El-Hewaity, 2014**).

The present work was to study the effect of flunixin meglumine on the pharmacokinetic aspects of tulathromycin after a single subcutaneous administration in healthy goats. Following subcutaneous administration of tulathromycin in a dose of 2.5mg/ kg b.wt. in goats, the serum concentration time curve was best fitted by a two - compartment open model. The drug was rapidly absorbed after subcutaneous administration with an absorption half-life $t_{0.5(\ abs)}$of 0.54 h. Our finding was similar to that reported for tulathromycin in calves 0.155 h **(Tohamy et al., 2011),** 0.2 h in rabbits (**Abo-El-Sooudet al., 2012).**The drug was detected in serum 5 minutes post injection and continued to increase gradually thereafter to reach its maximum concentration (C_{max}) 3.7ug/ ml at 0.98 hours post-injection and decrease gradually till reach its lower level (0.16 ug/ml) at 72 h. This result (C_{max}) was similarto that recorded for tulathromycin in ewes (3.598 ug/ ml) at 1.6 hours **(Washburn et al., 2014)**, in goats (1.0 and 1.2 ug/ml) at 1h **(Romanet et al., 2011**and**Cloither et al., 2011** respectively).

The serum tulathromycin concentration after coadministration with flunixin was lower than that after

tulathromycin administration alone form 0.083 to 6 hours after the injections. However, in thelater period for 8 to 72 hours following tulathromycin administration there is no difference in tulathromycin serum concentration between the two groups. The finding was similar to that reported by (**Ognio et al., 2005**) for enrofloxacin and flunixin in dogs. The drug was rapidly absorbed after SC administration with an absorption half-life $t_{0.5}(_{abs})$ of 0.34 h. (which was significantely ($P<0.05$) rapid than the result reported for the drug alone 0.54 h). This finding was similar to that reported by (**Tohamy, 2011)** for orbifloxacin with flunixin in buffalo calves (0.3 h), and (**El- Hewaity, 2014**) for cefepime with flunixin in goats (0.28 h). The elimination half-life $t_{0.5}(_{el})$ was 1.35 h for the alone treatment which similar to that reported with telithromycin in foals (3.81 h, **Javsicas et al., 2010**), tylosin in goats and sheep (271.39 and 282.46 min respectively, **Taha et al., 1999**) in camels (222.6min, **Ziv et al., 1995**) in cattle and buffaloes 2.24 and 2.4 h respectively **(saurit et al., 2002),** and that reported for erythromycin in sheep **(**3.15 h **Goudah et al., 2007),** but lower than that reported for the combination treatment (1.8 h). The in-vitro protein binding tendency of tulathromycin in goat's serum was (18.72 %) that result was lower than that reported by (**Nowakowski et al., 2004)** in cattle 40 %, in calve 38.86% (**Tohamy et al., 2011**) and that recorded in rabbits by (**Abo-El-Sooudet al., 2012**) 36%.

In conclusion, the obtained data clearly showed that flunixinaltered the kinetic behavior of tulathromycin after SC administration as it increase its absorption from injection site and delay the elimination that might cause reduction in the effectiveness of tulathromycin.

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