Journal homepage:
http://www.bsu.edu.eg/bsujournals/JVMR.aspx

Online ISSN: 2357-0520 Print ISSN: 2357-0512

Original Research Article

Subcutaneous pharmacokinetic interaction of tulathromycin With flunixin meglumine in goats

M. Adam, M. A. Tohamy, S.E. El-Sadek and Abeer M. Radi
Pharmacology Department, Faculty of Veterinary Medicine, Beni-Suef University, Egypt

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 3.7 µg /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 and 0.34 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.

ARTICLE INFO

Article history:

Received 11/ 2016

Accepted 12/2016

Online 12 /2016

Keywords:

Pharmacokinetics, Tulathromycin, Flunixin, Subcutaneous, Goats.

*Corresponding author. *Pharmacology Department, Faculty of Veterinary Medicine, Beni-Suef University, Egypt*. Tel: 01007236177

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 al., 2004; Retsemea & Fu, 2001).

Tulathromycin demonstrates better tissue penetration and longer half-lives than older macrolides due to its lipophilic properties (Benchaoui et al., 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 et al., 2007; Nutsch et al., 2005; Godinho et al., 2005; Skogerboe et al., 2005 and Robb et al., 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^{-1} tulathromycin subcutaneously (Clothieret al., 2011, Young et al., 2011; Grismer et al., 2014), while the 2nd was injected2.5 mg kg^{-1} tulathromycin with 2.2 mg kg^{-1} flunixin 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 µg ml^{-1} were prepared in antibiotic-free goat serum and phosphate buffer saline (pH 8). The minimal detectable limit for the assay method was 0.078 µg ml^{-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 (t 0.5(α)) 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 Snedecor and Cochran (1976).

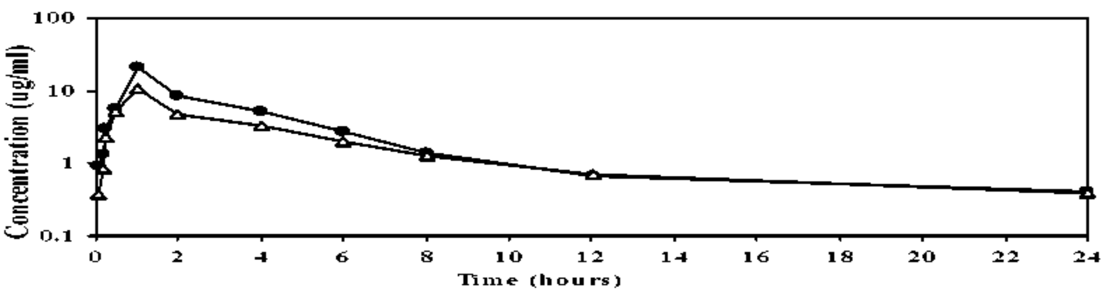

Figure (1): Semi-logarithmic graph depicting the time-concentration of tulathromycin in serum of goats after a single subcutaneous injection of 2.5 mg kg^{-1}b.wt alone (■) and with flunixin (A).

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 $t_{0.5(ab)}$ of 0.54 and 0.34 h and maximum serum concentrations (C_{max}) of 3.7 and 2.59 µg mł were achieved at (t_{max}) of 0.98 and 0.95 h., respectively. The elimination half-lives ($t_{0.5(el)}$) were 1.35 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 (µg.h.ml)	50.14±4.75	30.7±3.95***
AUMC (µg.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 $t_{0.5}(_{\alpha})$ 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}) 3.7 µg/ml at 0.98 hours post-injection and decrease gradually till reach its lower level (0.16 µg/ml) at 72 h. This result (C_{max}) was similarto that recorded for tulathromycin in ewes (3.598 µg/ml) at 1.6 hours **(Washburn et al., 2014)**, in goats (1.0 and 1.2 µg/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 $t_{0.5(ab)}$ 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.

References:

Abo-El-Sooud, K., Afifi, N. A. andAbd-El-Aty, A. M. (2012). Pharmacokinetics and bioavailability of tulathromycin following intravenous, intramuscular and subcutaneous administrations in healthy rabbits. Vet. World, 5(7):424-428.

Anderson, K.L., Hunt, E. and Davis, B.J. (1991). The influence of anti-inflammatory therapy on bacterial clearance following intramammary Escherichia coli challenge in goats. Veterinary Research Communications, 15, 147-161.

Arret, B.;Johnson, D.P. and Kirshbaum, A. (1971). Outline of details of microbiology assay of antibiotics. Second Revision, J.Pharm.Sci., 60:1690-1694.

Benchaoui, H.A., Nowakowski, M., Sherington, J., Rowan, T.G., and Sunderland, S.J. (2004): Pharmacokinetics and lung tissue concentrations of tulathromycin in swine.

Journal of Veterinary Pharmacology and Therapeutics, 27, 203-210.

Beretta, C., Garavaglia, G. andCavalli M. (2005). COX-1 and COX-2 inhibition in horse blood by phenylbutazone, flunixin, carprofen and meloxicam: an in vitro analysis. Pharmacological research, 52,302-306.

Brunton, L.L.; Laz, J.S. andParker, K.L. (2008). Goodman & Gilman's The Pharmacological Basis ofTherapeutics.11th Ed. Med. Pub. Div., N.Y., Chic., San Franc., Lisbon, Lond., pp: 1173.

Craig, A.W. and Suh, B. (1991). Protein binding and the antibacterial effects. Method for the determination of protein binding. In Antibiotics in laboratory Medicine, 3rd edn. Ed Lorian, V., pp., 367-402. Williams & Wilkins, Baltimore, Maryland,USA.

Cheng, Z., Nolan, A.M. and McKellar, Q.A. (1998). Measurement of cyclooxygenase inhibition in vivo: a study of two non-steroidal anti-inflammatory drugs in sheep. Inflammation, 22, 353-366.

Clothier, K.A., Leavens, T., Griffith, R.W., Wetzlich, S.E., Baynes, R.E., Riviere, J.E. and Tell, L.A. (2011). Pharmacokinetics of tulathromycin after single and multiple subcutaneous injections in domestic goats (Capra aegagrushircus). Journal of Veterinary Pharmacology and Therapeutics, 34, 448-454

Codony, R., Compano, R., Granados, M., Garcya-Regueiro, J.A. and Prat, M.D. (2002). Residue analysis of macrolides in poultry muscle by liquidchromatography-electrospray mass spectrometry.Journal of Chromatography A, 959: 131-141.

CVMP (Committee for Veterinary Medicinal Products), (2002):Tulathromycin summary report. European Medicines Agency Veterinary Medicines and Inspections; CVMP/0968/03.

El-Hewaity, M. (2014). Influence of Flunixin on the Disposition Kinetic of Cefepime in Goats.Advances in Pharmacological Sciences Volume 2014 , Article ID 471517, 5 pages

Evans, N.A. (2005). Tulathromycin: an overview of a new triamilide antibiotic for livestock respiratory disease. Veterinary Therapeutics: research in applied veterinary medicine, 6, 83-95.

Gibaldi, M. and Perrier, D. (1982). Pharmacokinetics, 2nd edn, pp., 409-424. MarcelDekker, New York.

Godinho, K.S.; Keane, S.G.; Nanjiani, I.A.; Benchaoui, H.A.; Sunderland, S.J.; Jones, M.A.; Weatherley, A.J.;Gootz, T.D.; and Rowan, T.G. (2005). Minimum inhibitory concentrations of tulathromycin against respiratory bacterial pathogens isolated from clinical cases in European cattle and swine and variability arising from changes in in vitro methodology. Veterinary Therapeutics: research in applied veterinary medicine, 6, 113-121.

Goudah, A., Sher Shah, S., Shin, H.C., Shim, J.H. and Abd El-Aty, A. M. (2007). Pharmacokinetics and Mammary Residual Depletion of Erythromycin in Healthy Lactating Ewes.J. Vet. Med. A 54, 607-611 Grismer B., Rowe J.D., Carlson J., Wetzlich S.E.andTell L.A.

(2014). Pharmacokinetics of tulathromycin in plasma and milk samples after a single subcutaneous injection in lactating goats (Capra hircus).Journal of veterinary pharmacology and therapeutics 37 :(2) 2058.

Javsicas L.H, Giguere S.andWomble A.Y. (2010). Disposition of oral telithromycin in foals and in vitro activity of the drug against macrolide- susceptible and macrolide-resistant Rhodococcusequi isolates. J Vet PharmacolTher.; 33(4):383-8.

Konigsson, K., Torneke, K., Engeland, I.V., Odensvik, K. and Kindahl, H. (2003). Pharmacokinetics and Pharmacodynamic Effects of Flunixin after Intravenous, Intramuscular and Oral Administration to Dairy Goats. Acta vet. scand., 44, 153-159.

Landoni, M.F., Cunningham, F.M. and Lees, P. (1995). Determination of pharmacokinetics and pharmacodynamics of flunixin in calves by use of pharmacokinetic/pharmaco-dynamic modelling. American Journal of Veterinary Research, 56, 786-794.

Leal, C., Codony, R., Compano, R., Granados, M. and Prat, M.D. (2001). Determination of macrolidesantibiotics by liquid chromatography. Journal of Chromatography A, 910: 285-290.

Letavic, M.A.; Bronk, B.S.; Bertsche, C.D. Casavant, J.M. ; Cheng, H.;Daniel, K.L.; George, D.M.; Hayashi, S.F.; Kamicker, B.J.; Kolosko, N.L.; Norcia, L.J.; Oberton, V.D.; Rushing, M.A. and Santoro, S.L. (2002). Synthesis and activity of a novel class of tribasic macrocyclic antibiotics: the triamilides. Bioorg. Med. Chem. Lett. 12: 2771-2774.

Mckellar, Q.A., Galbrath, E.A., Bogan, J.A., Russell, C.S., Hooke, R.E. and Lees, P. (1989). Flunixin pharmacokinetics and serum thromboxane inhibition in the dog. The Veterinary Record, 124, 651-654.

Nowakowski, M.A., Inskeep, P.B., Risk, J.E., Skogerboe, T.L., Benchaoui, H.A., Meinert, T.R., Sherington, J., and Sunderland, S.J. (2004). Pharmacokinetics and lung tissueconcentrations of tulathromycin, a new triamilide antibiotic, in cattle. Veterinary Therapy:research in applied veterinary medicine,(5) 60-74.

Nutsch, R.G.; Hart F.J; Rooney K.A; Weigel D.J; Kilgore W.R. and Skogerboe T.L. (2005). Efficacy of tulathromycin injectable solution for the treatment of naturally occurring swine respiratory disease. Vet. Ther., 6: 214-224.

Odensvik, K. and Magnusson, U. (1996). Effect of oral administration of flunixinmeglumine on the inflammatory response to endotoxin in heifers. American Journal of Veterinary Research, 57, 201-204.

Ogino, T., Mizuno, Y., Ogata, T., and Takahashi, Y., (2005). Pharmacokinetic interactions of flunixinmeglumine and enrofloxacin in dogs. American Journal of Veterinary Research 66, 1209-1213.

Rantala, M., Kaartinen, L., Valimaki, E., Stryrman, M., Hiekkaranta, M., Niemi, A., Saari, L., andPyorala, S. (2002). Efficacy and pharmacokinetics of enrofloxacin and flunixinmeglumine for treatment of cows with experimentally induced Escherichia coli mastitis. Journal of Veterinary Pharmacology and Therapeutics, 25, 251-258. Retsemea, J. and Fu, W. (2001). Macrolides; Structures and microbial targets. International Journal of Antimicrobial Agents, 18, S3-S10. Richeson, J.T.; Beck, P.A.; Gadberry, M.S.; Gunter, S.A.; Hess, T.W;Hubbell, D.S. and Jones, C. (2008). Effects of on-arrival versus delayed modified live virus vaccination on health, performance, and serum infectious bovine rhinotracheitis titers of newly received beef calves. Journal of Animal Science. 86:999-1005.

Romanet J, Smith GW, Leavens TL, Baynes RE, Wetzlich SE, Riviere JE, and Tell LA (2012). Pharmacokinetics and tissue
elimination of tulathromycin following subcutaneous administration in meat goats. American journal of veterinary research, 73(10): 1634-1640. Robb, E.J.; Tucker C.M., Corley L., Bryson W.L. and Rogers K.C. (2007). "Efficacy of tulathromycin versus enrofloxacin for initial treatment of naturally occurring bovine respiratory disease in feeder calves". Vet. Ther.; 8: 127-135.

Saurit A.R., Rubio M., Baroni E., San A.M., Sanchez S., andBoggio J.C. (2002). Some comparative aspects of the pharmacokinetics of tylosin in buffaloes and cattle. Vet Res Commun.; 26(1):49-54. Skogerboe, T.L.; Rooney, K.A.; Nutsch, R.G.; Weigel, D.J.; Gajewski, K. and Kilgore, W.R. (2005). Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated bovine respiratory disease in feedlot cattle. Vet. Ther., 6: 180-196. Snedecor, G.W. and Cochran, W.G. (1976). Statistical methods. 6th Ed. Ames, Iowa, USA, pp.,502-503.

Taha, A. A., A. E. Elsheik, A. E. Khalafalla, I. A. M. Osman, and A.Salam Abdullah, (1999). Disposition kinetics of tylosin administered intravenously and intramuscularly in desert sheep and nubian goats. Vet. J. 158, 210-215.

Tohamy, M.A.(2011). pharmacokinetic interactions of flunixin and orbifloxacin in buffalo calves. Insight pharmaceutical sciences 1 (3): 2933.

Tohamy, M.A., El-Gendy, A.A..M, andTaha, A.Attia (2011). Some pharmacokinetic aspects of tulathromycin in Fresian cattle calves.Journal of American Science7(5): 651-655.

Venner, M.; Kerth R. and Klug, E. (2007). Evaluation of tulathromycin in the treatment of pulmonary abscesses in foals. Vet. J., 174: 418- 421. Washburn K., Fajt V.R., Coetzee J.F., Rice S., Wulf L.W., andWashburn S. (2014). Pharmacokinetics of tulathromycin in nonpregnant adult ewes. Journal of veterinary pharmacology and therapeutics : 37 pg

Welsh, E.M. and Nolan, A.M. (1995). Effect of flunixinmeglumine on the thresholds to mechanical stimulation in healthy and lame sheep. Research in Veterinary Science, 58, 61-66

Whittem, T., Firth, E.C., Hodge, H., and Turner, K., (1996). Pharmacokinetic interactions between repeated dose phenylbutazone and gentamicin in the horse. Journal of Veterinary

Pharmacology and Therapeutics 19, 454-459**.**

Young, G., Smith, G.W., Leavens, T.L., Wetzlich, S.E., Baynes, R.E.,Mason, S.E., Riviere, J.E. and Tell, L.A. (2011). Pharmacokinetics of tulathromycin following subcutaneous administration in meat goats. Research in Veterinary Science, 90, 477479.

Ziv G., Creveld C.V., Ben-Zvi Z., Glickman A., andYagil R. (1995). Disposition kinetics of tylosin tartrate administered intravenously and intramuscularly to normal and water-deprived camels. J Vet PharmacolTher.; 18(4):299-305.