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Effect of tulathromycin on abomasal emptying rate in healthy lactating goats

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ABSTRACT

Tulathromycin is a long-acting semi-synthetic macrolide antibiotic that is synthesized from erythromycin. Macrolides have pharmacodynamic properties beyond their antimicrobial effects, including anti-inflammatory and immunomodulatory properties that are perceived to be clinically beneficial. An additional pharmacodynamic property of macrolides is a prokinetic effect, which is marked in adult cattle and calves administered erythromycin and less prominent in calves administered spiramycin, tilmicosin, and tylosin. Based on structural similarities to erythromycin, the hypothesis was that parenteral administration of tulathromycin would increase abomasal emptying rate in healthy adult goats. Accordingly, five adult lactating goats (30–36 months of age) received each of the following 3 treatments: IM injection of 2 mL of 0.9% NaCl (control); IM injection of tulathromycin (2.5 mg/kg body weight); IV injection of tulathromycin (2.5 mg/kg body weight). Abomasal emptying rate was assessed by acetaminophen absorption, which was injected into the abomasum through a surgically placed abomasal cannula at 50 mg/kg BW, 15 min after each treatment. Jugular venous blood samples were obtained periodically after injection and plasma acetaminophen concentrations determined using a colorimetric nitration assay. The maximum observed plasma acetaminophen concentration (Actual C_{max}) and time of actual C_{max} (Actual T_{max}) were determined, and pharmacokinetic modeling was used to calculate model C_{max} and model T_{max} and abomasal emptying half-time (T50). Results showed that tulathromycin (IM and IV) increased abomasal emptying rate, as indicated by a shorter time to actual T_{max} and model T_{max}, and shorter T50, than control. The clinical relevance of these findings remains to be determined.

1. Introduction

Macrolides are a group of chemically related compounds whose antimicrobial activity stems from the presence of a large macrocyclic lactone ring to which one or more deoxy sugars, usually desosamine and cladinose, are attached (Giguère et al., 2006). The original member of the group, erythromycin was isolated from the soil borne bacteria *Streptomyces erythreus* in 1952. Other macrolides are derived from related bacteria (e.g., tylosin) or by chemical modification of the original compounds (e.g., tulathromycin) using fermentation under optimized conditions followed by organic synthesis. Macrolides are categorized according to the number of macrocyclic lactone ring components as 12-membered, 13-membered,

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14-membered, 15-membered, and 16-membered groups (Giguère et al., 2006). Tulathromycin is a novel long-acting semi-synthetic macrolide antibiotic of the triamilide group that has been available since 2004 for use in veterinary medicine. Tulathromycin is an equilibrated mixture of a 15-membered (90%, isomer A) and 13-membered (10%, isomer B) macrocyclic ring with a unique chemical structure consisting of 3 polar amine groups (European Medicines Agency, 2002; Evans, 2005). Tulathromycin is a broad-spectrum antimicrobial, with in vitro activity against certain gram-negative and gram-positive bacteria, including the bacterial pathogens most commonly associated with bovine and swine respiratory disease (Norcia et al., 2004).

Macrolides have pharmacodynamic properties beyond their antimicrobial effects, including anti-inflammatory and immunomodulatory properties that are perceived to be clinically beneficial (Giguère et al., 2006; Buret, 2010; Fischer et al., 2011). An additional pharmacodynamic property of macrolides is a prokinetic effect, which is marked in adult cattle and calves administered erythromycin (Wittek and Constable, 2005; Nouri and Constable, 2007; Wittek et al., 2008a,b) and less prominent in calves administered spiramycin (Rashnavadi et al., in press), tilmicosin (Nouri and Constable, 2007), and tylosin (Nouri and Constable, 2007). Based on structural similarities to erythromycin, particularly the presence of an amino-sugar at C-5 of the macrocyclic lactone ring, we hypothesized that parenteral administration of tulathromycin would increase abomasal emptying rate in healthy adult goats. Preliminary support for this hypothesis was provided by a recent study in milk-fed calves that demonstrated tulathromycin exerted a weak prokinetic effect (Rashnavadi et al., in press). We investigated our hypothesis using healthy adult goats that had a surgically placed abomasal cannula.

2. Materials and methods

2.1. Animals

Five adult lactating Zaraibi (Egyptian Nubian) goats weighing 20–22 kg and aged from 30 to 36 months were obtained from local farms. Goats were housed together at Cairo University in one large indoor stall and fed fresh cut Berseem clover (*Trifolium alexandrinum*, also known as Egyptian clover) and ad libitum concentrate mixture of corn (75%), barley (15%), and molasses (10%) with free access to food and water. Goats were milked by hand once a day. The health of all goats was monitored before and throughout the experimental period by periodic physical examination and monitoring of feed consumption and fecal characteristics.

2.2. Drugs

Tulathromycin (DRAXXIN®, Pfizer, Animal Health Division, Cairo, Egypt) was obtained as a ready to use, sterile, aqueous, colorless solution in 20 mL vials. Each milliliter of tulathromycin contained 100 mg of tulathromycin as free base in 50% propylene glycol vehicle, monothioglycesol (5 mg/mL), and citric acids and hydrochloric acids added to adjust pH.

Acetaminophen (paracetamol; Zhejiang Kangle Pharmaceutical Co., Ltd., Zhejiang China) was obtained as a white, fine powder that was sparingly soluble in water.

2.3. Experimental design

Goats had been used in a study to characterize the pharmacokinetics of tulathromycin (Amer et al., 2012) and subsequently had an abomasal cannula surgically placed as described (Ahmed et al., 2005). Goats were housed for four weeks after surgery to permit recovery. Food, but not water, was removed overnight for 12 h and injections were administered in the morning. Each goat received a single IM injection of 1 mL 0.9% NaCl (negative control). One week later, goats received an IV injection of tulathromycin (2.5 mg/kg BW) into the right jugular vein using a needle and syringe after clipping the venipuncture site and scrubbing with tincture of iodine (2.5%). Six weeks later goats received an IM injection of tulathromycin (2.5 mg/kg BW) into the semimembranosus muscle; the duration between tulathromycin injections was to ensure adequate clearance of tulathromycin, based on an estimated mean half-life after IV injection of 4.1 days in these goats (Amer et al., 2012) and 2.5–4.6 days after SC injection in juvenile and market aged goats (Clothier et al., 2011; Young et al., 2011; Romanet et al., 2012). A wash out period of a week was considered adequate for complete clearance of acetaminophen, based on pharmacokinetic studies in cattle (Grochowina and Janus, 2007; Ehsani-Kheradgerdi et al., 2011) and sheep (Sharifi et al., 2009).

Acetaminophen (50 mg/kg body weight in 10 mL of 0.9% NaCl solution containing 1 drop of 99% absolute methanol to enhance solubility) was injected into the abomasum through the abomasal cannula at a dose of 15 min after injection of tulathromycin or negative control. Plasma tulathromycin concentrations were near their maximal value at this time after IM administration (Amer et al., 2012).

Venous blood samples (5 mL) were collected from the jugular vein of each goat immediately before treatment was administered (time = 0 min) and at 5, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 150, 180, and 240 min after the start of injection into the abomasum. These sampling times were selected in an attempt to have at least 6 data points before and after the time of maximal acetaminophen concentration in order to facilitate nonlinear regression analysis for pharmacokinetic modeling. Blood samples were collected into 6 mL tubes containing sodium fluoride and potassium oxalate, centrifuged at 3000 × *g* for 15 min, and 2 mL of plasma harvested and stored at −20 °C until analysis for determination of acetaminophen concentration.

2.4. Sample analysis and pharmacokinetic modeling

Plasma was thawed at approximately at 25 °C and analyzed spectrophotometrically by use of a colorimetric nitration assay as described (Marshall et al., 2005). The maximum observed plasma concentration (Actual C_{max}) and time of maximum observed plasma concentration (Actual T_{max}) were obtained from a plot of the plasma acetaminophen concentration – time data. Changes in plasma acetaminophen concentrations over time were analyzed using commercially available software (SAS 9.2, SAS Inc., Cary NC; WinNonLin, Pharsight Corp., Cary NC). A 1-compartment model with first order elimination could not be fit to the plasma acetaminophen concentration–time data.

Noncompartmental analysis of an extravascular input was therefore applied using commercially available software (Model 200; WinNonLin, Pharsight Corp., Cary NC); this approach calculates the area under the curve using a linear trapezoid method to the last sample time and extrapolation to infinity as the ratio of last measured plasma concentration and the terminal slope of the plasma concentration versus time curve. Mean residence time was calculated from the noncompartmental analysis using standard equations.

Pharmacokinetic analysis was also performed using the first derivative of Siegel's modified power exponential formula, as previously described (Marshall et al., 2005). The equation was derived from the fact that the acetaminophen concentration-versus-time curve represented as a cumulative dose curve is an inverse analog of the scintigraphic curve with the following equation: $C(t) = m \times k \times \beta \times e^{-k \times t} \times (1 - e^{-k \times t})^{\beta - 1}$, where $C(t)$ is the acetaminophen concentration in plasma at a specified time point, t is time, m (units of {μg/mL} × min) is the area under acetaminophen concentration–time curve when time is infinite, k (units of min^{-1}) is an estimate of the rate constant for abomasal emptying, β is a constant that provides an estimate of the duration of the lag phase before an exponential rate of emptying is reached, and e is the natural logarithm. Nonlinear regression was used to estimate values for m, k, and β as described (Marshall et al., 2005). Values for model C_{max} and model T_{max} were obtained by fitting the estimated values for k, β, and m in the nonlinear equation to the cumulative dose curve equation for acetaminophen. The abomasal half emptying time (T50) was calculated by fitting the estimated values for k and β to the following equation: $T50 = (-1/k) \times \ln(1 - 2^{-1/\beta})$ (Marshall et al., 2005).

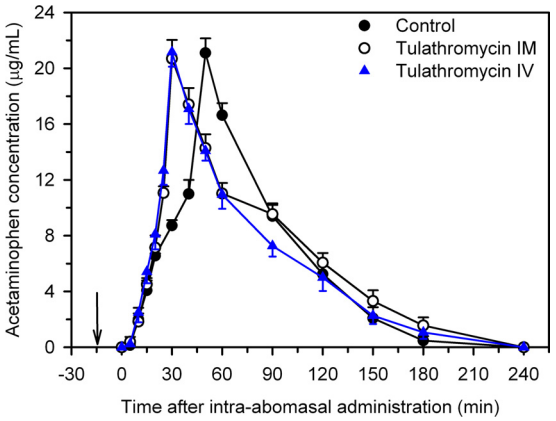

Fig. 1. Mean ± standard deviation (SD) of the plasma acetaminophen concentration in 5 lactating goats after treatment with tulathromycin (2.5 mg/kg BW, IM, open circles), tulathromycin (2.5 mg/kg BW, IV, blue triangles), or a negative control (2.0 mL of 0.9% NaCl solution IM, filled circles) at time = −15 min (arrow) using a crossover design. Goats were administered acetaminophen (50 mg/kg BW) through an abomasal cannula 15 min after treatments were administered.

2.5. Statistical analysis

Data were expressed as mean ± SD and a value of $P < 0.05$ was considered significant. Repeated measures ANOVA, with repeated measures on treatment and time, was used to determine the main effects of treatment and time and the interaction between treatment and time. Variables with non-normal distributions were log transformed or ranked before statistical analysis was performed. Bonferroni adjusted post tests were conducted to compare acetaminophen absorption test factors after tulathromycin IM injection to control, tulathromycin IV injection to control, and tulathromycin IM to tulathromycin IV, whenever the F test value was significant, producing a P value for a significant post-test of <0.0167. A statistical software program was used for all statistical comparisons (SAS 9.2, SAS Institute Inc., Cary, NC).

3. Results

Intravenous and IM injection of tulathromycin increased the rate of abomasal emptying when compared to control (Table 1, Fig. 1), as indicated by a shorter time to actual T_{max} ($P < 0.001$) and model T_{max} ($P < 0.001$), and a shorter half emptying time (T50). Actual C_{max} and model C_{max} were similar for all 3 treatments.

Mean values for the total cumulative absorption of acetaminophen when time is infinite (m) approximated those for AUC (Table 1).

4. Discussion

The major finding of this study was that IV and IM injection of tulathromycin increased the rate of abomasal emptying in healthy goats as assessed by acetaminophen absorption pharmacokinetics. This finding was consistent with those of a recent study in milk-fed calves (Rashnavadi et al., in press) but inconsistent with long held beliefs that only 14-membered macrolides (such as erythromycin) have prokinetic activity (Itoh et al., 1985).

Tulathromycin is a semisynthetic derivative of erythromycin that is prepared by fermentation followed by organic synthesis (EMEA, 2002; Evans, 2005). Erythromycin produces a marked prokinetic effect in calves (Wittek and Constable, 2005; Nouri and Constable, 2007; Rashnavadi et al., in press) and adult cows (Wittek et al., 2008a,b) most likely by acting as a motilin-receptor agonist via binding to motilin receptors in the pyloric antrum and proximal portion of the small intestine (Itoh, 1997). Motilin is a 22 amino acid peptide that is periodically released from endocrine cells in the duodenojejunal mucosa, thereby initiating the migrating motor complex of the mammalian gastrointestinal tract during the interdigestive period. There is considerable interest in the therapeutic applications of motilin agonists, referred to as the motilides (i.e., motilin-like macrolides), that share a common binding site in the third transmembrane region of the motilin receptor (Itoh, 1997). Motilide activity is influenced primarily by modifications to the N-dimethylamino group at the 3′ position of the amino sugar (desosamine) bound at C-5 of the ring and by the presence of a neutral sugar (cladinose) at C-3 that is parallel to the amino sugar at C-5 (Itoh et al., 1985; Sunazuka et al., 1989; Tsuzuki et al., 1989; Xu et al., 2005). Erythromycin has a 14-membered macrocyclic ring with a dimethylamino sugar (desosamine) at C-5 and a neutral sugar (cladinose) at C-3 (Tsuzuki et al., 1989; Xu et al., 2005). For comparison, tulathromycin has a 13 or 15-membered macrocyclic ring with a desosamine sugar at C-5 and a modified cladinose sugar at C-3 (EMEA, 2004). It therefore appears that the prokinetic effect of tulathromycin results from the type and location of sugars attached to the macrocyclic ring.

Tulathromycin is labeled for the treatment of bovine and swine respiratory disease in a single dose at 2.5 mg/kg bodyweight when administered SC or IM as a full course therapy. We have reported that the pharmacokinetics of a single IM injection of tulathromycin (2.5 mg/kg of BW) in lactating goats are similar to those in ruminating cattle administered a single SC injection of tulathromycin (2.5 mg/kg of BW). On this basis, it is likely that tulathromycin is effective in treating respiratory disease in goats. Tulathromycin (2.5 mg/kg, SC or intralesional) has also been administered as part of the treatment of caseous lymphadenitis in goats and sheep (Washburn et al., 2009). The results of the study reported here in healthy goats indicate that a potentially added benefit of tulathromycin administration in sick goats could be an increased abomasal emptying rate, but appropriately conducted field studies are required to confirm this expectation. It is important to emphasize that it is inappropriate to administer an antimicrobial for a non-antimicrobial effect (such as increasing abomasal emptying rate), as such use may unnecessarily promote the development of antimicrobial resistance.

Acetaminophen absorption pharmacokinetic values are widely used as an index of gastric emptying and have been validated against the gold standard method (scintigraphy) in humans (Clements et al., 1978), horses (Lohmann et al., 2000) and suckling calves (Marshall et al., 2005). The main advantages of the acetaminophen absorption technique are its low cost, wide availability, and ease of assay (Clements et al., 1978). The prokinetic effect of

Table 1
Abomasal emptying rate indices of 5 lactating goats after treatment with tulathromycin (2.5 mg/kg BW, IM), tulathromycin (2.5 mg/kg BW, IV), or a negative control (2.0 mL of 0.9% NaCl solution IM) at time = −15 min (arrow) using a crossover design. Abomasal emptying rate was assessed by acetaminophen absorption (50 mg/kg BW), which was administered through an abomasal cannula 15 min after treatments were administered. Actual C_{max} is the maximal plasma acetaminophen and Actual T_{max} is the time at which Actual C_{max} occurred. Values for Model C_{max}, Model T_{max}, k, β, and m were obtained by fitting a nonlinear equation to the cumulative dose curve for acetaminophen (see Section 2 for details). T50 is the abomasal emptying half-time. AUC is the total area under the concentration–time curve after acetaminophen administration. Data are means ± SD.

Factor	Control	Tulathromycin IM	Tulathromycin IV	*P* value: *F* test treatment
Actual C_{max} (μg/mL)	21.1 ± 1.0	20.7 ± 1.3	21.2 ± 1.0	0.75
Actual T_{max} (min)	50 ± 0	30 ± 0*	30 ± 0*	NE
AUC (μg × min/mL)	1346 ± 85	1455 ± 130*,†	1319 ± 109	0.0042
Mean residence time (min)	70.5 ± 1.7	71.8 ± 2.0†	66.2 ± 2.8*	0.0009
Model C_{max} (μg/mL)	16.9 ± 0.5	16.4 ± 1.0	17.3 ± 0.7	0.31
Model T_{max} (min)	53.6 ± 0.6	44.4 ± 1.3*,†	39.5 ± 1.8*	<0.0001
T50 (min)	68.2 ± 0.5	60.9 ± 2.6*,†	52.2 ± 3.8*	<0.0001
k (min^{-1})	0.0299 ± 0.0014	0.0283 ± 0.0026†	0.0367 ± 0.0070	0.026
β	4.99 ± 0.97	3.52 ± 0.32*	4.32 ± 0.80	0.0070
m (μg × min/mL)	1384 ± 85	1353 ± 137†	1147 ± 147*	0.0012

NE, not estimable.
* $P < 0.0167$ compared to control.
† $P < 0.0167$ compared to tulathromycin IV.

tulathromycin in healthy goats was demonstrated by a shorter time to actual T_{max} and model T_{max}, as well as a shorter abomasal emptying half-time (T50), than control. The elimination half time of acetaminophen in this study appeared to be shorter than that reported for cattle (Grochowina and Janus, 2007; Ehsani-Kheradgerdi et al., 2011) and lambs (Sharifi et al., 2009). This result in consistent with a more active metabolism in goats than in cattle or sheep, with goats having a significantly higher activity of UDP-glucuronyltransferase (Short et al., 1988) and higher liver concentrations of cytochrome p-450, NADPH cytochrome c reductase, aldrin epoxidase, aminopyrine N-demethylase, ethoxycoumarin O-deethylase, microsomal and cytosolic stilbene oxide (epoxide) hydrolase and glutathione s-transferase than sheep and cattle (Wisniewski et al., 1987). Acetaminophen is metabolized primarily by conjugation with sulfate and glucuronide and in goats the glucuronide metabolite is the predominant moiety in plasma (Ali et al., 1996).

Thus in case of respiratory infection in goats, tulathromycin not only can achieve a full course therapy by single IM injection, but also, its acceleration effect on the abomasal emptying rate can reduce anorexia, abolished daily weight gain and thus economic loss, Moreover it can be used for hypomotility disorder.

5. Conclusion

In conclusion, the results of this study indicated that IM and IV injection of tulathromycin at 2.5 mg/kg BW increased the rate of abomasal emptying in goats, as measured by acetaminophen absorption pharmacokinetics. Although the clinical relevance of our findings remains to be determined, the parenteral administration of the related prokinetic macrolide, erythromycin, increased milk production and rumen contraction rate in the immediate post-operative period in cattle undergoing surgical correction of left displaced abomasum (Wittek et al., 2008a) or abomasal volvulus (Wittek et al., 2008b).

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship that could inappropriately influence or bias the content of the paper.

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