Pharmacokinetics of erythromycin in nonlactating and lactating goats after intravenous and intramuscular administration

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The objectives of this work were to compare the pharmacokinetics of erythromycin administered by the intramuscular (i.m.) and intravenous (i.v.) routes between nonlactating and lactating goats and to determine the passage of the drug from blood into milk. Six nonpregnant, nonlactating and six lactating goats received erythromycin by the i.m. (15 mg/kg) and the i.v. (10 mg/kg) routes of administration. Milk and blood samples were collected at predetermined times. Erythromycin concentrations were determined by microbiological assay. Results are reported as mean ± SD. Comparison of the pharmacokinetic profiles between nonlactating and lactating animals after i.v. administration indicated that significant differences were found in the mean body clearance (8.38 ± 1.45 vs. 3.77 ± 0.83 mL/kg·h respectively), mean residence time (0.96 ± 0.20 vs. 3.18 ± 1.32 h respectively), area under curve from 0 to 12 h (AUC_{0-12}) (1.22 ± 0.22 vs. 2.76 ± 0.58 µg·h/mL respectively) and elimination half-life (1.41 ± 1.20 vs. 3.32 ± 1.34 h); however, only AUC_{0-12} showed significant differences after the i.m. administration. Passage of erythromycin in milk was high (peak milk concentration/peak serum concentration, 2.06 ± 0.36 and $AUC_{0-12\text{milk}}/AUC_{0-12\text{serum}}$, 6.9 ± 1.05 and 2.37 ± 0.61 after i.v. and i.m. administrations respectively). We, therefore, conclude that lactation affects erythromycin pharmacokinetics in goats.

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INTRODUCTION

Clinical or subclinical intramammary infections in lactating goats produce important economical losses. In decreasing order of frequency, *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci and enterobacteria have been reported as aetiological agents in clinical mastitis, whereas coagulase-negative staphylococci and secondarily *S. aureus* are the most prevalent agents in subclinical mastitis (Bergonier *et al.*, 2003).

Erythromycin is a macrolide antibiotic with good antibacterial effect on gram-positive cocci as staphylococci and streptococci. Erythromycin inhibits the bacterial protein synthesis by binding to the 50S ribosomal unit (Brisson-Noel *et al.*, 1988). The bactericidal action of the macrolides is time-dependent, thus, the serum concentrations must remain over the *MIC* for a successful therapy. The *T* > *MIC* is considered the most accurate pK/pD index of efficacy (McKellar *et al.*, 2004), however, as macrolide tissue concentrations are well above the serum concentrations,

this ratio never attains high values (den Hollander *et al.*, 1998). Optimal dosage recommendations should be prepared on the basis of tissue or body fluids pharmacokinetics (Burrows *et al.*, 1989).

Systemically administered antibiotics for mastitis rely on the penetration of the drug from the blood into the udder. This passage takes place mostly by passive diffusion, thus, only the nonionized, lipid-soluble, protein unbound molecules can penetrate the blood–milk barrier. As erythromycin is a weak base, with a pKa of 8.7–8.8, the pH difference between blood and milk favours its trapping in milk, even in mastitis where milk pH may rise up to 7.5.

The pharmacokinetics of erythromycin has been studied in serum and tissues of healthy and pneumonic calves (Burrows *et al.*, 1989), foals (Lakritz *et al.*, 2000) and rats (Kohno *et al.*, 1989); however, to our knowledge, there is a very little information of the pharmacokinetics and milk penetration of erythromycin after its administration to goats. As the pharma-

cokinetics of antibiotics may change in lactating animals (Oukessou *et al.*, 1990; Petracca *et al.*, 1993; Rule *et al.*, 1996), the objectives of this study were to compare the pharmacokinetics of erythromycin administered by the intramuscular (i.m.) and intravenous (i.v.) routes between nonlactating and lactating goats and to determine the passage of the drug from blood into milk.

MATERIALS AND METHODS

Animals

These experiments were approved by the Institutional Animal Care and Use Committee of the Faculty of Veterinary Science.

Six nonpregnant, nonlactating goats weighing 24.5 ± 4.46 kg (range, 20–30 kg) (experiment one), and six nonpregnant lactating goats (30 days postpartum) weighing 28.17 ± 3.31 kg (range, 24–33 kg) (experiment two), were used. The daily milk production was 177.8 ± 88.61 mL and the somatic cell count was $\leq 500\,000$ cells/mL as determined using the California Mastitis Test. The animals used in both experiments were either in their first or second lactation. All animals were healthy as determined by clinical examination and blood and serum biochemical analysis. During acclimatization for 3 weeks, and the subsequent treatment periods, the animals were kept outside, they were grazed on natural pasture and had access to water *ad libitum*.

Experimental design

Experiment one (nonlactating goats): the animals received i.v. (10 mg/kg) and i.m. (15 mg/kg) erythromycin. A crossover design was used (three i.v. and three i.m.). The wash-out interval between administrations was 1 week.

Experiment two (lactating goats): the animals received i.v. (10 mg/kg) and i.m. (15 mg/kg) erythromycin. A crossover design was used (three i.v. and three i.m.). The wash-out interval between administrations was 1 week.

In both experiments, for the i.v. and i.m. administrations, erythromycin (Pantomicina®, Laboratorio Abbot, Madrid, Spain) was diluted in saline solution to 150 mg/mL and a single dose was administered either into the right jugular vein or between the semimembranous and semitendinous muscles.

In both experiments blood samples were collected from the left jugular vein at 0, 0.08, 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h after the i.v. administration and at 0, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 h after the i.m. drug administration.

Blood samples were allowed to clot at room temperature and centrifuged at 2500 *g*, for 10 min. The serum was stored at 4 °C until analysis.

In experiment two, the udder was emptied completely before the administration of the drug and milk samples were obtained at 0, 2, 4, 6, 8, 10, 12 and 24 h after both i.v. and i.m. administrations. At each time, both half udders were completely milked, immediately the milk obtained from each half udder was homogenized and a 2.5-mL aliquot was taken for erythromycin concentration determination. Total milk volume from each goat was recorded to enable calculation of the fraction of the dose excreted in milk. Samples were stored at 4 °C until analysis. All serum and milk samples were assayed not later than 3 days after collection. The stability of the drug in spiked samples stored at 4 °C for up to 4 days was assessed.

Analytical method

Concentrations of erythromycin in serum and milk samples were determined by microbiological assay (Bennet *et al.*, 1966) using *Micrococcus luteus* ATCC 9341 as test organism. Standard curves of the drug were prepared in free antibiotic pooled from goat serum or milk. Each sample was measured in triplicate. Inhibition zones around the sample wells were measured with a digital gauge and compared with inhibition zones produced by the standards. The quantification limit was 0.024 µg/mL. The inter and intra-assay coefficients of variation were less than 6.7% and 5.9% respectively; the method was linear between 0.024 and 12.5 µg/mL ($r = 0.9921$), for both serum and milk standards.

Pharmacokinetic analysis

The erythromycin serum concentration–time curves were analysed by nonlinear least-squares regression analysis using PCNonlin 4.0 (SCI Software, Lexington, KY, USA).

Erythromycin serum disposition curves after i.v. administration were best fit to a polyexponential equation (Eqn 1):

$$C_{(t)} = Y_i^{(-\lambda_i t)}, \tag{1}$$

where $C_{(t)}$ is the serum concentration at time t; Y_i (µg/mL) is the coefficient of the ith term and $\lambda_i t$ (h) is its exponent.

Initial estimates were determined using the residual method (Gibaldi & Perrier, 1982) and refitted by nonlinear regression.

The number of exponents needed for both i.v. and i.m. administrations data were determined by Akaike criterion (Yamahoka *et al.*, 1978).

For the i.v. route a biexponential model was chosen according to an open bicompartmental model in all the animals (Eqn 2):

$$C_{(t)} = Y_1^{(-\lambda_1 t)} + Y_2^{(-\lambda_2 t)}, \tag{2}$$

where $C_{(t)}$ (µg/mL) represents erythromycin serum concentration at time t; Y_1 and Y_2 (µg/mL) are the extrapolated concentrations to time 0 of the first and second phase of erythromycin serum disposition, respectively, and λ_1 and λ_2 (per h) are the distribution and elimination slopes respectively.

Erythromycin serum disposition curves after i.m. administration were analysed following the same procedure as used for i.v. analysis. According to Akaike criterion (Yamahoka *et al.*, 1978), disposition curves were best fit to a biexponential equation and explained by an open monocompartmental model with first-order absorption in all the goats (Eqn 3):

$$C_{(t)} = \left[\text{Dose} \times \frac{K_{ab}}{V_d}(K_{ab} - K_{el})\right]e^{-K_{el}t} - e^{-K_{ab}t}, \qquad (3)$$

where V_d is the volume of distribution, K_{ab} and K_{el} are the rates of absorption and elimination respectively.

Most pharmacokinetic parameters were calculated using classic equations (Gibaldi & Perrier, 1982). AUC_{0-12} and area under the first moment curve ($AUMC_{0-12}$) were calculated by the trapezoidal rule. Erythromycin i.m. bioavailability (F) was calculated as (Eqn 4):

$$F(\%) = \left(\frac{AUC_{0-12\ i.m.}}{AUC_{0-12\ i.v.}}\right)\left(\frac{\text{Dose}_{i.v.}}{\text{Dose}_{i.m.}}\right) \times 100, \qquad (4)$$

where $AUC_{0-12i.m.}$ and $AUC_{0-12i.v.}$ are the areas under the drug concentration–time curves for the i.m. and i.v. administrations respectively; $\text{Dose}_{i.v.}$ and $\text{Dose}_{i.m.}$ are the i.v. and i.m. doses of erythromycin respectively.

The passage of erythromycin from blood into milk after i.v. and i.m. treatments was calculated and expressed as (Eqn 5) and (Eqn 6):

$$\frac{AUC_{0-12\ milk}}{AUC_{0-12\ serum}}, \qquad (5)$$

where $AUC_{0-12\ milk}$ and $AUC_{0-12\ serum}$ are the areas under the drug concentration–time curves for milk and serum from 0 to 12 h respectively;

$$\frac{C_{max\ milk}}{C_{max\ serum}}, \qquad (6)$$

where $C_{max\ milk}$ and $C_{max\ serum}$ are the observed maximum erythromycin concentrations after i.m. administration for milk and serum respectively. Data were presented as mean ± SD.

Statistical analysis

The statistical analysis was performed using the spss® 12.0 software package (SPSS Inc., Chicago, IL, USA). The differences between the serum pharmacokinetic parameters of nonlactating and lactating goats for both routes of administration were determined by the nonparametric Mann–Whitney test. A value of $P \leq 0.05$ was considered significant.

RESULTS

Treatment-related side effects were not seen in any of the goats, however, animals injected intramuscularly manifested a transient pain in the site of injection. Mean serum and milk concentration–time curves for erythromycin after i.v. and i.m. administrations to nonlactating and lactating goats are presented in Figs 1 & 2 respectively. No erythromycin concentrations were detected at the 24 h postadministration sample. Pharmacokinetic serum values are summarized in Tables 1 & 2. Erythromycin concentrations in the serum decreased in a biexponential manner after i.v. administration in both groups, indicating the presence of distribution and elimination phases
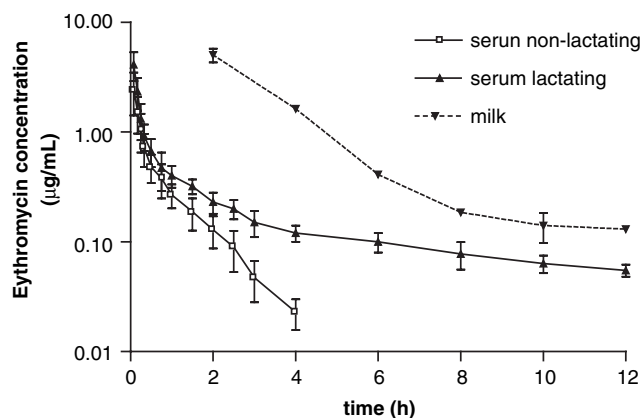

Fig. 1. Serum and milk concentration–time curves for erythromycin after i.v. administration at a dosage of 10 mg/kg to nonlactating and lactating goats (each group, $n = 6$).
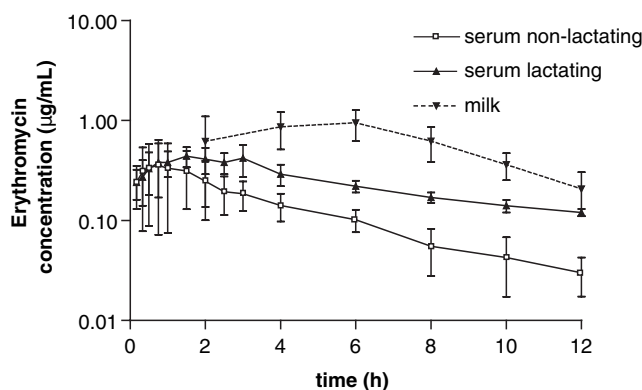

Fig. 2. Serum and milk concentration–time curves for erythromycin after i.m. administration at a dosage of 15 mg/kg to nonlactating and lactating goats (each group, $n = 6$)

and justifying the use of a two-compartment kinetic model for analysing the data.

Comparison of the pharmacokinetic profiles between nonlactating and lactating animals after i.v. administration indicated that significant differences were found in the mean body clearance (Cl_b) (8.38 ± 1.45 vs. 3.77 ± 0.83 mL/kg·h respectively), mean residence time (MRT) (0.96 ± 0.20 vs. 3.18 ± 1.32 h respectively), AUC_{0-12} (1.22 ± 0.22 vs. 2.76 ± 0.58 µg·h/mL respectively) and elimination half-life ($t_{1/2(el)}$) (1.41 ± 1.20 vs. 3.32 ± 1.34 h) (Table 1).

Erythromycin serum disposition curves after i.m. administration were best fit to a monocompartmental open model with first order absorption in both nonlactating and lactating goats. Comparison of the pharmacokinetic profiles between nonlactating and lactating animals indicated that erythromycin was extensively absorbed as reflected by the high F, 94.30 ± 28.17% and 95.36 ± 27.58% for both groups respectively. As with the i.v. treatment, AUC_{0-12} was lower in nonlactating goats than in lactating ones (1.70 ± 0.25 vs. 3.77 ± 0.58 µg·h/mL respectively) (Table 2). Nonsignificant differences were found between

Table 1. Mean (± SD) serum pharmacokinetic parameters for erythromycin after i.v. administration at a dosage of 10 mg/kg to nonlactating and lactating goats (each group, $n = 6$)

Pharmacokinetic parameter	Nonlactating goats	Lactating goats
C_1 (µg/mL)	2.99 ± 1.53	7.07 ± 4.46*
C_2 (µg/mL)	0.52 ± 0.31	0.41 ± 0.15[ns]
λ_1 (per h)	8.71 ± 4.25	7.18 ± 2.70[ns]
λ_2 (per h)	0.67 ± 0.27	0.24 ± 0.10*
$AUC_{(0-12)}$ (µg·h/mL)	1.22 ± 0.22	2.76 ± 0.58*
$t_{1/2(d)}$ (h)	0.12 ± 0.10	0.11 ± 0.06[ns]
$t_{1/2(el)}$ (h)	1.41 ± 1.20	3.32 ± 1.34*
K_{10} (per h)	2.91 ± 1.25	2.69 ± 1.39[ns]
K_{12} (per h)	3.85 ± 2.58	4.05 ± 1.44[ns]
K_{21} (per h)	2.62 ± 2.23	0.68 ± 0.32[ns]
V_c (L/kg)	3.28 ± 1.40	1.68 ± 0.74[ns]
$C_{p(0)}$ (µg/mL)	3.52 ± 1.42	7.49 ± 4.56[ns]
Cl_b (L/kg·h)	8.38 ± 1.45	3.77 ± 0.83*
MRT (h)	0.96 ± 0.20	3.18 ± 1.32*
$V_{d(ss)}$ (L/kg)	8.04 ± 2.29	11.84 ± 4.96[ns]

C_1, C_2, y-axis intercept terms; λ_1, distribution rate constant; λ_2, elimination rate constant; $AUC_{(0-12)}$, area under the serum concentration vs. time curve from 0 to 12 h; $t_{1/2(d)}$, distribution half-life; $t_{1/2(el)}$, elimination half-life; K_{10}, central compartment elimination rate constant; K_{12}, rate constant for passage from central to peripheral compartment; K_{21}, rate constant for passage from peripheral to central compartment; V_c, volume of central compartment; $C_{p(0)}$, serum concentration at time 0; Cl_b, body clearance; MRT, mean residence time; $V_{d(ss)}$, volume of distribution at steady state; ns, not significantly different; *significantly different ($P \leq 0.05$).

Table 2. Mean (± SD) serum pharmacokinetic parameters for erythromycin after i.m. administration at a dosage of 15 mg/kg to nonlactating and lactating goats (each group, $n = 6$)

Pharmacokinetic parameter	Nonlactating goats	Lactating goats
K_a (per h)	6.98 ± 5.45	2.32 ± 2.40[ns]
K_{el} (per h)	0.29 ± 0.11	0.20 ± 0.10[ns]
$t_{1/2(a)}$ (h)	0.26 ± 0.35	0.67 ± 0.61[ns]
$t_{1/2(el)}$ (h)	2.63 ± 1.00	3.89 ± 1.16[ns]
T_{max} (h)	0.77 ± 0.65	1.64 ± 0.75[ns]
C_{max} (µg/mL)	0.41 ± 0.17	0.49 ± 0.09[ns]
$AUC_{(0-12)}$ (µg·h/mL)	1.70 ± 0.25	3.77 ± 0.58*
F (%)	98.83 ± 28.95	95.36 ± 27.58[ns]

K_a, absorption rate constant; K_{el}, elimination rate constant; $t_{1/2(a)}$, absorption half-life; $t_{1/2(el)}$, elimination half-life; T_{max}, time of maximum concentration; C_{max}, serum maximum concentration; $AUC_{(0-12)}$, area under the serum concentration vs. time from 0 to 12 h; F, bioavailability; ns, not significantly different; *significantly different ($P \leq 0.05$).

nonlactating and lactating goats for the rest of the pharmacokinetic parameters.

Pharmacokinetic milk parameters are summarized in Table 3. Erythromycin penetrated rapidly and extensively from blood into milk after both i.v. and i.m. treatments. Concentrations of erythromycin measured in milk after i.v. and i.m. administrations were higher than those measured in plasma at all sampling times. The calculated $AUC_{0-12milk}/AUC_{0-12serum}$ values were 6.93 ± 1.05 and 2.37 ± 0.61 for i.v. and i.m. administrations,

Table 3. Mean (±SD) milk pharmacokinetic parameters for erythromycin after i.v. and i.m. administrations at a dosage of 10 and 15 mg/kg, respectively, to lactating goats ($n = 6$)

Pharmacokinetic parameter	i.v. administration	i.m. administration
$T_{max\ milk}$ (h)	2.00 ± 0.00	5.00 ± 1.67
$C_{max\ milk}$ (µg/mL)	5.03 ± 1.25	1.20 ± 0.45
$AUC_{(0-12)}$ (µg·h/mL)	14.51 ± 2.44	7.00 ± 2.30
$T_{1/2(el\ milk)}$ (h)	1.35 ± 0.33	2.76 ± 0.52
$C_{max\ milk}/C_{max\ serum}$		2.06 ± 0.36
$AUC_{0-12milk}/AUC_{0-12serum}$	6.93 ± 1.05	2.37 ± 0.61

$T_{max\ milk}$, time of maximum milk concentration; $C_{max\ milk}$, maximum milk concentration; $AUC_{(0-12)}$, area under the milk concentration vs. time from 0 to 12 h; $T_{1/2(el\ milk)}$, milk elimination half-life; $C_{max\ milk}/C_{max\ serum}$, observed maximum milk concentration/observed maximum serum concentration; $AUC_{0-12milk}/AUC_{0-12serum}$, area under the milk concentration vs. time from 0 to 12 h/area under the serum concentration vs. time from 0 to 12 h.

respectively, and $C_{max\ milk}/C_{max\ serum}$ value was 2.06 ± 0.36 for the i.m. treatment. Only a minimal proportion of the administered drug was eliminated by the udder (0.085 ± 0.033% and 0.027 ± 0.011% for the i.v. and i.m. routes respectively).

DISCUSSION

Pharmacokinetics of erythromycin after i.v. and i.m. administrations

Serum erythromycin disposition curves after i.v. administration were best fit to an open bicompartmental model in all the animals of both groups, which is in accordance with the results reported for foals (Lakritz *et al.*, 1999).

The drug was widely distributed in the organism, the large values of volume of distribution at steady state [$V_{d(ss)}$] in both nonlactating (8.04 ± 2.29 L/kg) and lactating (11.84 ± 4.96 L/kg) goats show a wide extent in tissue penetration. Similar high levels of tissue passage have been reported after i.v. erythromycin administration to foals, however, $V_{d(ss)}$ values were lower in this species (2.66 ± 0.20 L/kg) (Lakritz *et al.*, 1999), physiological and age differences may account for this result. High volumes of distribution have been reported for macrolides as tylosin (3.12 ± 0.34 L/kg) (Taha *et al.*, 1999) and azalides as azithromicin (34.52 ± 9.21 L/kg) (Cárceles *et al.*, 2005) after i.v. administration to goats.

After the i.m. administration, all erythromycin disposition curves were best fit to an open monocompartmental model, in agreement with previous reported data on healthy calves (Burrows *et al.*, 1989). Erythromycin bioavailability after i.m. administration was high (98.83 ± 28.95% and 95.36 ± 27.58% in nonlactating and lactating goats respectively), similar values of bioavailability (84 ± 11%) were also determined after i.m. administration of tylosin to lactating goats (Taha *et al.*, 1999). Absorption was fast ($T_{max} < 2$ h) for both nonlactating and lactating animals. Blood concentrations were low, this is in accordance with previous reports after intragastric (Lakritz *et al.*, 1999) and oral (Lakritz *et al.*, 2000) erythromycin

administration to foals and after i.m. erythromycin administration to calves (Burrows *et al.*, 1989).

Pharmacokinetics of erythromycin in milk

Xenobiotics cross the blood–milk barrier by passive diffusion, thus, the basic nature of macrolides favours its trapping in the udder, as milk pH is lower than that of blood. Our results show that erythromycin milk concentrations were higher than serum concentrations at all the milk sampling points, in accordance, the $AUC_{0-12\text{milk}}/AUC_{0-12\text{serum}}$ and $C_{\text{max milk}}/C_{\text{max serum}}$ ratios were >1 for both i.v. and i.m. treatments. Other macrolide, tilmicosin, has also shown a high passage from blood into milk after its i.v. administration to goats (Ramadan, 1997). In our study only a minimal amount of the administered dose was excreted by this route, thus, the udder could not be considered as an important route of erythromycin elimination.

In order to obtain a successful clinical outcome, erythromycin concentrations must be above the *MIC* for the causative agent at least during half of the dosing interval (Van Bambeke & Tulkens, 2001). Previous research reported *MIC* of erythromycin against *S. aureus* of ruminant origin is 0.50 μg/mL (Prescott, 2002). Higher MIC_{90} was determined for *S. aureus* and coagulase-negative staphylococci obtained from bovine mastitis in Argentina (0.75 μg/mL) (Gentilini *et al.*, 2000, 2002). Our results show that at these doses, milk erythromycin concentrations could provide therapeutic levels for the treatment of susceptible micro-organisms with *MIC* ≤ 0.5 μg/mL for 4 and 8 h after i.v. and i.m. administrations respectively. However, for extrapolating the results of this study to the clinical practice, milking should have been performed twice a day.

Comparative pharmacokinetics of erythromycin between nonlactating and lactating goats

Previous studies have demonstrated that lactation may affect pharmacokinetics, as the udder may constitute an additional peripheral compartment. This was shown in the case of lipophilic drugs that are capable of reaching high concentrations in milk (Petracca *et al.*, 1993; Shem-Tov *et al.*, 1997).

The lower *AUC*, $t_{1/2(\text{el})}$ and *MRT* and higher Cl_b found in the nonlactating group may be due to modifications in the distribution and/or elimination of erythromycin, as both processes are involved in the above-mentioned parameters. No differences were found for V_d; however, the high variability observed for this parameter may account for this result. Erythromycin is eliminated primarily by hepatic cytochrome P450 (CYP3A) metabolism. Hepatic oxidation of xenobiotics may be impaired during lactation, as many physiological processes shift towards the production of milk, e.g. producing large amounts of fatty acids, which are increased in serum during lactation.

Erythromycin is known to bind predominantly to alpha-1-acid-glycoprotein (AGP) in pigs and humans (Kinoshita *et al.*, 1995). It has been previously reported that changes in the AGP serum concentration affect the pharmacokinetics of drugs, due to modifications in the drug plasma protein binding. Cl_b increased while *AUC* decreased significantly when erythromycin was administered to pigs with lower AGP plasma concentration (Kinoshita *et al.*, 1995). This may be due to the enhanced erythromycin elimination, as the unbound fraction increases (Kinoshita *et al.*, 1995). Erythromycin has low hepatic extraction, thus clearance is inversely related to the unbound fraction of the drug. To our knowledge, no studies have been performed of AGP concentration in lactating and nonlactating goats, however, in lactating women increased AGP concentrations were demonstrated (Fleishaker *et al.*, 1989). If higher AGP concentrations were found in lactating goats, the decrease in Cl_b observed in our study could be related, at least partially, to higher binding of erythromycin to proteins. On the other hand, antibiotic trapping in the milk may cause the udder to work as a deep compartment, decreasing the serum clearance, as it has been previous reported for ceftazidime in lactating cows (Rule *et al.*, 1996).

Our results show that lactation affects serum erythromycin pharmacokinetics, thus further studies should be performed to determine if these differences occur in drug tissue disposition.

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