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Pharmacokinetics of erythromycin after intravenous, intramuscular and oral administration to cats

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ABSTRACT

The aim of this study was to characterise the pharmacokinetic properties of different formulations of erythromycin in cats. Erythromycin was administered as lactobionate (4 mg/kg intravenously (IV)), base (10 mg/kg, intramuscularly (IM)) and ethylsuccinate tablets or suspension (15 mg/kg orally (PO)). After IV administration, the major pharmacokinetic parameters were (mean ± SD): area under the curve $(AUC)_{(0-\infty)}$ 2.61 ± 1.52 μg h/mL; volume of distribution (V_z) 2.34 ± 1.76 L/kg; total body clearance (Cl_t) 2.10 ± 1.37 L/h kg; elimination half-life ($t_{½\lambda}$) 0.75 ± 0.09 h and mean residence time (MRT) 0.88 ± 0.13 h. After IM administration, the principal pharmacokinetic parameters were (mean ± DS): peak concentration (C_{max}), 3.54 ± 2.16 μg/mL; time of peak (T_{max}), 1.22 ± 0.67 h; $t_{½\lambda}$, 1.94 ± 0.21 h and MRT, 3.50 ± 0.82 h. The administration of erythromycin ethylsuccinate (tablets and suspension) did not result in measurable serum concentrations. After IM and IV administrations, erythromycin serum concentrations were above minimum inhibitory concentration $(MIC)_{90}$ = 0.5 μg/mL for 7 and 1.5 h, respectively. However, these results should be interpreted cautiously since tissue erythromycin concentrations have not been measured and can reach much higher concentrations than in blood, which may be associated with enhanced clinical efficacy.

Introduction

Erythromycin is a macrolide antibiotic active against many Gram-positive cocci (*Staphylococcus intermedius, S. aureus*, Streptococci), some strains of *Pasteurella* spp., *Mycoplasma* spp., *Bordetella bronchiseptica* and a number of anaerobic organisms. It is the drug of choice in treating *Campylobacter jejuni* enteritis (Papich and Riviere, 2001; Giguère, 2006).

Erythromycin's minimum inhibitory concentration (MIC) for the most susceptible bacteria (namely, staphylococci, streptococci, *Corynebacterium* spp., *Campylobacter* spp., anaerobic bacteria, *Chlamydia/Chlamydophila*) is ⩽0.5 μg/mL, although some staphylococci strains may be much less sensitive (Giguère, 2006). The therapeutic efficacy of erythromycin depends on the maintenance of concentrations above the MIC of susceptible micro-organism on which it produces a time-dependent bacteriostatic effect. At concentrations much higher than the MIC (which may be attained in some tissues) erythromycin can produce a bactericidal effect. Newer macrolides (clarithromycin, azithromycin) have an antibacterial efficacy that correlates better with the area under the concentration–time curve/MIC (AUC/MIC), but for erythromycin the time above MIC (T > MIC) is considered the most accurate pharmacokinetic/pharmacodynamic index of efficacy (Toutain et al., 2002; McKellar et al., 2004; Lees et al., 2006).

Erythromycin is widely used and has been extensively studied in human medicine (Patamasucon et al., 1981; Bérubé et al., 1988; Croteau et al., 1988) and in some domestic animal species (Soback et al., 1987; Burrows et al., 1989a,b; Eriksson et al., 1990; Ewing et al., 1994; Bohlen et al., 1995; Lakritz et al., 1999, 2000; Ambros et al., 2007; Albarellos et al., 2008). It is a highly lipid-soluble weak base with a pK_a of 8.8 and is widely distributed throughout the body. However, erythromycin is inactivated in the acidic environment of the stomach so chemical modifications of the molecule (esterification or addition of salts) are necessary to prevent inactivation and to improve oral (PO) absorption. Esterified erythromycin, such as ethylsuccinate, is absorbed intact from the gastrointestinal tract and must be hydrolysed in blood to release the active free base (Papich and Riviere, 2001). This process can be incomplete, leading to variable absorption rates and erratic erythromycin serum concentrations in humans and animals (Bérubé et al., 1988; Croteau et al., 1988; Eriksson et al., 1990; Ewing et al., 1994; Albarellos et al., 2008).

The objective of the current study was to characterise the pharmacokinetic profiles of different erythromycin formulations administered to cats by the intravenous (IV), intramuscular (IM) and oral (PO) routes.

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Materials and methods

Experimental animals

All animal procedures were approved by the Institutional Animal Care and Use Committee, School of Veterinary Science, University of Buenos Aires, Argentina. The experimental animals comprised five adult mixed breed cats, three females and two males, weighing 6.04 ± 2.11 kg. All cats were healthy as determined by clinical examination, complete blood and serum biochemical and urine analysis. The animals were housed in the School of Veterinary Medicine, University of Buenos Aires, facilities. Access to high quality commercial dry food (Fit 32, Royal Canin) and water was ad libitum.

Dosage forms

Erythromycin was administered IV as an aqueous 15% erythromycin lactobionate solution (Pantomicina, Abbott Laboratories); IM as a 20% solution of erythromycin base (Eritromicina 20%, Burnet), and PO as ethylsuccinate, formulated as tablets (500 mg base equivalent, Pantomicina, Abbott Laboratories), and 8% suspension (Pantomicina, Abbott Laboratories).

Experimental design

The study was designed in two phases (experiments A and B). In both experiments, the animals were fasted overnight before antibiotic administration. In experiment A the animals received single doses of erythromycin lactobionate (4 mg/kg IV via the cephalic vein), and erythromycin base (10 mg/kg IM into the dorsal lumbar muscles) in a cross-over design. A 3-week washout period was allowed to elapse between administration routes.

In experiment B, 1 month after experiment A, the same cats received single PO administrations of erythromycin ethylsuccinate (15 mg/kg) as tablets or PO suspension in a cross-over design. A 3-week washout was allowed to elapse between the two dosage forms.

Blood sampling

A jugular vein was catheterised 24 h before each study as previously described (Albarellos et al., 2003). For IV administration, blood samples (0.7 mL) were withdrawn at the following post-administration times: 0, 0.083, 0.16, 0.33, 0.5, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00 and 12.00 h. For the IM and oral administrations an additional sample was taken at 14.00 h.

Blood samples were allowed to clot at room temperature and centrifuged at 1500 *g* for 15 min. The supernatant serum was frozen at −20 °C until analysis. Serum samples were assayed during the week following collection.

Erythromycin analytical method

Erythromycin serum concentrations were determined by microbiological assay (Bennet et al., 1966) using *Micrococcus luteus* ATCC 9341 as the test micro-organism. Standard curves were prepared in normal cat serum between 0.024 and 12.5 μg/mL erythromycin concentrations. Each sample was seeded in triplicate and each standard dilution in quintuplicate.

The method was linear between 0.024 and 12.50 μg/mL ($r = 0.9938$). Inter- and intra-assay coefficients of variation were 6.68% and 5.75%, respectively. The limits of detection and quantification of the method were 0.024 μg/mL and 0.048 μg/mL, respectively. The limit of quantification was the lower limit of concentration used in the pharmacokinetics analysis.

Pharmacokinetic analysis

A non-compartmental approach based on statistical moments (Gibaldi, 1984) using the PCNONLIN 4.0 software (SCI Software) was used to calculate the basic pharmacokinetic parameters in individual cats after intravascular and extravascular administrations of erythromycin. The mean residence time (MRT) of erythromycin was calculated from the equation:

$$\mathrm{MRT} = \frac{\sum_0^\infty \mathrm{tCpdt}}{\sum_0^\infty \mathrm{Cpdt}}$$

where $\sum_0^\infty$Cpdt is the area under the plasma concentration time curve, AUC, and $\sum_0^\infty$tCpdt is the first moment of the plasma concentration time curve, AUMC (Gibaldi and Perrier, 1982); MRT is an estimate of the mean time for one intact molecule to transit through the body; AUC_{0-t} was calculated using the linear trapezoidal rule (Baggot, 1978); $AUC_{0-\infty}$ was calculated as C_t/λ_z, where C_t is the last measured concentration and λ_z is the elimination rate constant; the value of λ_z was obtained from final serum concentrations and terminal slopes determined for least-squares fit to data from the terminal portion of the curves (Gibaldi and Perrier, 1982). Total body clearance, Cl_t, was calculated as Dose/AUC. Volume of distribution, V_z, was calculated as Cl_t/λ_z. The mean absorption time (MAT) after extravascular administrations was estimated for the difference between MRT for extravascular and intravenous administration. The peak concentration (C_{max}) and time of peak (T_{max}) were the observed values. The time serum concentration of erythromycin remained above the MIC_{90} ($T > MIC_{90}$) was determined graphically from the previously reported MIC_{90} values for Gram-positive cocci (≈0.5 μg/mL) (Giguère, 2006), and was expressed as percentage of the dose interval (Toutain et al., 2002; McKellar et al., 2004). All values were reported as means ± SD.

Statistical analysis

Statistical analysis of the differences between pharmacokinetic parameters was performed applying a paired Student's *t* test. The significance level was $P \leqslant 0.05$.

Results

Adverse effects were not observed during or following erythromycin IV administration in any of the experimental animals. One cat manifested signs of gastrointestinal upset (vomiting) 1 h after oral administration of erythromycin suspension. After IM administration, moderate pain was apparent in all the animals, though inflammation signs were not observed in any of them. The oral administration of erythromycin ethylsuccinate formulated as tablets or suspension, was very low and erratic. Although erythromycin was detected in serum from 0.16 to 6 h post-administration concentrations were always near the limit of quantification of the analytical method.

The mean serum disposition curves following the IV and IM erythromycin administrations are presented in Fig. 1. The pharmacokinetic parameters calculated for each route of administration are summarised in Table 1. After IV administration, erythromycin distributed widely with an apparent V_z of 2.34 ± 1.76 L/kg. The antibiotic was rapidly cleared from the serum with a Cl_t of 2.10 ± 1.37 L/h kg, λ_z of 0.93 ± 0.11/h, a terminal half-life of 0.75 ± 0.09 h and an MRT of 0.88 ± 0.13 h. Erythromycin absorption after IM administration was slow with a MAT of 2.40 ± 0.71 h. Elimination half-life and MRT were significantly longer than after IV administration (1.94 vs. 0.75 h). However, no statistically significant differences were observed for Cl_t and V_z, which indicated that the longer half-life was due to the slow rate of absorption ('flip/flop' phenomenon).

Time above MIC for erythromycin after IM administration was, for the most susceptible bacteria (MIC_{90} 0.5 μg/mL), approximately 7 h, representing 29% or 58% of the dosing interval on a once or

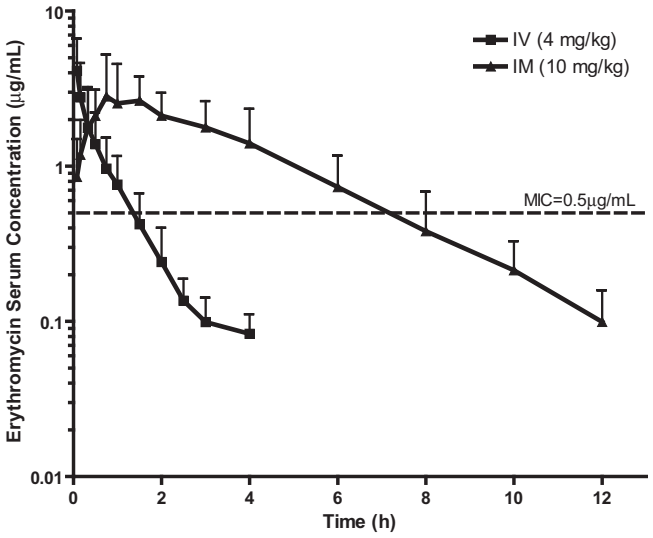

Fig. 1. Erythromycin serum concentration–time profile (mean ± SD) after IV (4 mg/kg) (■) and IM (10 mg/kg) (▲) administration to cats.

Table 1
Means (±SD) of pharmacokinetic parameters for erythromycin following IV (4 mg/kg) and IM (10 mg/kg) administration to cats.

Pharmacokinetic parameter	Intravenous administration (4 mg/kg) (mean ± SD)	Intramuscular administration (10 mg/kg) (mean ± SD)
C_{max} (μg/mL)	6.20 ± 3.77	3.54 ± 2.16
t_{max} (h)	–	1.22 ± 0.67
$AUC_{(0-last)}$ (μg h/mL)	2.53 ± 1.51	12.09 ± 6.41
$AUC_{(0-\infty)}$ (μg h/mL)	2.61 ± 1.52	12.32 ± 6.43
V_z (L/kg)	2.34 ± 1.76	4.38 ± 3.49
λ_z (/h)	0.93 ± 0.11	0.36 ± 0.04*
Cl_t (L/h kg)	2.10 ± 1.37	1.62 ± 1.32
$t_{½\lambda}$ (h)	0.75 ± 0.09	1.94 ± 0.21*
MRT (h)	0.88 ± 0.13	3.50 ± 0.82*
MAT (h)	–	2.40 ± 0.71
F (%)	–	96 ± 61

C_{max}, peak serum concentration; t_{max}, time to reach peak serum concentration; $AUC_{(0-last)}$, area under the serum concentration time curve from time zero to last sample point; $AUC_{(0-\infty)}$, area under the serum concentration time curve from time zero to infinity; V_z, apparent volume of distribution (in the IM administration is the value corrected by bioavailability); λ_z, apparent terminal rate constant; Cl_t, total body clearance (in the IM administration is the value corrected by dose, bioavailability and half-life); $t_{½\lambda}$, terminal half-life; MRT, mean residence time; MAT, mean absorption time.
* Significantly different ($P \leqslant 0.05$).

twice daily schedule, respectively. After IV administration, $T > MIC$ was approximately 1.5 h corresponding to 19% of the dosing interval on a three times daily schedule.

Discussion

Gastrointestinal side effects were not observed in the present study. It seemed that cats were more resistant to the emetic effect of erythromycin compared with dogs receiving the same oral formulations (Albarellos et al., 2008). In fact, a higher susceptibility of the gastrointestinal motility to this drug in dogs has been reported (Itoh et al., 1984). Another explanation could be the increment on lower oesophageal sphincter pressure caused by erythromycin in cats that is not seen in dogs (Hall and Washabau, 1997).

In the present study, AUC and derived pharmacokinetic parameters (V_z and Cl_t) showed important inter-individual variation. The inter-subject variation in the plasma disposition for erythromycin after systemic administration is well known and has been reported in many species, including humans (Austin et al., 1980), dogs (Albarellos et al., 2008), calves (Burrows et al., 1989b) and horses (Lakritz et al., 1999). The causes of this variability were not clear, but may be related to the complex interactions of erythromycin with transport systems, such as P-glycoprotein and OATP, and cytochrome P450 3A. Although it has not been reported in cats, the double role of erythromycin as substrate/inhibitor of P-glycoprotein (Kurnik et al., 2006; Liu et al., 2003) and OATP (Ayrton and Morgan, 2001; Seithel et al., 2007) as well as of cytochrome P450 3A (Touchette and Slaughter, 1991; Polasek and Miners, 2006) could explain, at least partially, the differences between subjects on the pharmacokinetic behaviour of this antimicrobial.

Another cause could be related to the uptake and efflux of erythromycin in polymorphonuclear (PMN) cells. It has been established that some macrolides (erythromycin, clarithromycin, telithromycin) are moderately taken up by PMN in a rapid but saturable manner, with a very high individual variability, especially in the kinetics of uptake (Bosnar et al., 2005).

Following IV administration to cats the extent of distribution was very wide, as reflected by the large V_z. This was not unexpected since most macrolides (in most species) have V_z larger than 1 L/kg (Soback et al., 1987; Bohlen et al., 1995; Lakritz et al., 1999; Ambros et al., 2007; Albarellos et al., 2008). In fact, a V_z for azithromycin in cats was reported to be 23 L/kg (Hunter et al., 1995). Erythromycin elimination in cats is faster than in most species, such as calves, goats and dogs (Soback et al., 1987; Bohlen et al., 1995; Ambros et al., 2007; Albarellos et al., 2008), but not horses (Lakritz et al., 1999).

After IM administration, erythromycin absorption was moderate and slow (MAT 2.40 h; T_{max} 1.22 ± 0.67 h; C_{max} 3.54 ± 2.16 μg/mL). Bioavailability (96%) reflected an almost complete absorption but this parameter should be cautiously interpreted since the experimental design was not a randomised cross-over trial and the applied doses were not the same for the three assayed administration routes. The delay in the absorption process is reflected in the long terminal slope. The lack of statistically significant differences in Cl_t and V_z after IV and IM administration could be reflecting a 'flip/flop' phenomenon. In fact, 'flip/flop' kinetics has been reported for erythromycin in horses (Clark, 2008) after IM and oral administration and in calves (Burrows et al., 1989b) after IM and SC administration.

Although oral erythromycin formulations (ethylsuccinate solution and tablets) were administered at a higher dose than when IV or IM routes were used, absorption was very poor and irregular. These results agree with previous studies performed in humans and other animals. Low PO absorption of erythromycin esters (ethylsuccinate) in humans has been well described (Patamasucon et al., 1981; Bérubé et al., 1988; Croteau et al., 1988). In a study performed in horses, erythromycin ethylsuccinate was not absorbed in half of the assayed animals, whilst plasma concentrations were very low in the remainder (C_{max} 0.3 μg/mL) (Ewing et al., 1994). A study in dogs where erythromycin ethylsuccinate was administered orally (formulated as tablets or suspension) found poor absorption, especially when tablets were used (Albarellos et al., 2008). It is possible that erythromycin ethylsuccinate ester needs the presence of food in the gastrointestinal system to facilitate hydrolysis and absorption, such as was seen in cats administered palmitate esterified chloramphenicol (Watson, 1991, 1992).

Since former macrolides (such as erythromycin) have a time-dependent bactericidal effect, the ideal dosing regimen should maximise the duration of exposure. The $T > MIC$ is the parameter that best correlates with efficacy. Maximum killing is seen when the time above MIC is at least 50% of the dosing interval (Van Bambeke and Tulkens, 2001; Toutain et al., 2002; McKellar et al., 2004). In the present study, this goal was not achieved, although erythromycin has been reported to be as efficacious for treating infectious diseases in cats and dogs (skin, respiratory system) (Greene et al., 2008; Norsworthy et al., 2009). The discrepancy could be explained because of their ability to concentrate in tissue having high tissue/plasma concentration rates with favourable clinical outcomes.

Conclusions

The results of this study showed that dose rates of erythromycin during IV or PO routes were insufficient and led to a decline in plasma concentrations and potential inefficacy. IM dosage produced relatively greater plasma concentrations, but the effective dose interval should be no longer than 12 h. Further studies are required to correlate pharmacokinetic data (such as tissue/serum concentrations) with clinical evidence, and this will be necessary to establish dosage regimens and to minimise the risk of bacterial resistance.

Conflict of interest statement

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

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