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Pharmacokinetics and skin concentrations of lincomycin after intravenous and oral administration to cats

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The aim of the present study was to describe the plasma pharmacokinetic profile and skin concentrations of lincomycin after intravenous administration of a 15% solution and oral administration of 300 mg tablets at a dosing rate of 15 mg/kg to cats. Susceptibility of staphylococci (n = 31) and streptococci (n = 23) strains isolated from clinical cases was also determined. Lincomycin plasma and skin concentrations were determined by microbiological assay using *Kocuria rhizophila* ATCC 9341 as test microorganism. Susceptibility was established by the antimicrobial disc diffusion test. Individual lincomycin plasma concentration–time curves were analysed by a non-compartmental approach. After intravenous administration, volume of distribution, body clearance and elimination half-life were 0.97 L/kg ± 0.15 L/kg, 0.17 L/kg ± 0.06 L/h.kg and 4.20 h ± 1.12 h, respectively. After oral administration, peak plasma concentration, time of maximum plasma concentration and bioavailability were 22.52 µg/mL ± 10.97 µg/mL, 0.80 h ± 0.11 h and 81.78% ± 24.05%, respectively. Two hours after lincomycin administration, skin concentrations were 17.26 µg/mL ± 1.32 µg/mL (intravenous) and 16.58 µg/mL ± 0.90 µg/mL (oral). The corresponding skin: plasma ratios were 2.08 ± 0.47 (intravenous) and 1.84 ± 0.97 (oral). The majority of staphylococci and streptococci tested in this study were susceptible to lincosamides (87.09% and 69.56%, respectively). In conclusion, lincomycin administered orally at the assayed dose showed a good pharmacokinetic profile, with a long elimination half-life and effective skin concentration. Therefore, it could be a good first option for treating skin infections in cats.

Introduction

Lincomycin is, as clindamycin, a lincosamide antibiotic mainly active against staphylococci, streptococci and anaerobic bacteria (Giguère 2006). It is recommended for treating skin and other soft tissue infections produced by susceptible bacteria in dogs and cats (Papich & Riviere 2009). Lincosamides are antibiotics classified as 'important' (instead of 'critically important' or 'highly important') based on their importance in human medicine (WHO 2005, cited by Collignon, Courvalin & Aidara-Kane 2008) and would therefore be a better alternative to other antibiotics for the treatment of bacterial infections in animals (Collignon *et al.* 2008).

Lincomycin achieves therapeutic concentrations in most body tissues (Giguère 2006) and is widely metabolised in the liver to inactive metabolites that are eliminated through bile and urine (Brown *et al.* 1975; Hornish, Gosline & Nappier 1987).

Lincomycin pharmacokinetics have been studied in calves (Burrows, Barto & Weeks 1986), pigs (Kuroha, Son & Shimoda 2001; Nielsen & Gyrd-Hansen 1998), sheep (Ziv & Sulman 1973), goats (Abo El-Sooud, Goudah & Abd El-Aty 2004), chickens (Soback *et al.* 1987) and cats (Albarellos *et al.* 2012). However, to the authors' knowledge there is no published information on lincomycin pharmacokinetic behaviour after oral administration in cats.

The aim of this study was to characterise the plasma pharmacokinetic profile and skin concentrations of lincomycin after intravenous and oral administration in domestic cats.

Materials and methods

Experiment animals

Experimental animals were five adult (5-year-olds) mixed-breed cats, with an average weight of 4.95 kg ± 0.55 kg. All cats were healthy, as determined by clinical examination, complete blood and plasma biochemical analysis and urinalysis. Animals were housed in facilities at the Faculty of Veterinary Medicine, University of Buenos Aires and allowed to acclimatise for two months before the experiment. Access to a high-quality commercial dry food (Royal Canin®, Argentina) and water was available *ad libitum* before the study. All animal procedures were approved by the Institutional Animal Care and Use Committee, School of Veterinary Science, University of Buenos Aires, Argentina.

Dosage form

A 15% lincomycin aqueous solution (Tritonyl inyectable®, Triton Vet S.R.L., Argentina) was used for intravenous administration. The dose (15 mg/kg) was half diluted with saline (NaCl 0.9%) before administration and infused over a 3 min period. For the oral administration, marked 300 mg lincomycin tablets (Tritonyl 300®, Triton Vet S.R.L, Argentina) were used. Each animal received 75 mg (each tablet was divided into quarters).

Experiment design

The study was carried out in a randomised cross-over design with a two week washout period.

Lincomycin was administered intravenously (15 mg/kg) through a 24G catheter (Abbocath-T®, Venisystems™, Abbott, Ireland) placed into the cephalic vein. For oral administration, a quarter tablet was administered per cat (actual dose of 15.19 mg/kg ± 1.65 mg/kg). Cats were deprived of access to food for 12 h prior to the study and up to 6 h post administration.

Blood sampling

For blood collection, a jugular vein was catheterised 24 h before each study according to a technique described previously (Albarellos *et al.* 2003).

The same blood sampling schedule was used for both phases of the study. Blood samples (0.7 mL) were collected through the jugular catheter prior to antibiotic administration and at the following post-administration times: 5 min, 10 min, 20 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h and 12 h.

Samples were collected into heparinised tubes, mixed and placed on ice until plasma separation 30 min later. Plasma was separated after centrifugation (1500 g, 15 min) and stored at –20 °C until analysis. All samples were assayed in the week after collection.

Skin sampling

Skin samples (1 cm^2) were collected under general anaesthesia (tiletamine/zolazepam 10 mg/kg, Zelazol, Fort Dodge, Pfizer S.R.L., Argentina) from the loose skin over the shoulders two hours after lincomycin was administered (either intravenously or orally). Samples were rinsed briefly with saline solution, dried with sterile gauze, weighed and stored at –20 °C.

To avoid heat inactivation of the antibiotic, skin samples were carefully and slowly cut to small pieces (≈1 mm^3). Lincomycin was eluted using the technique described by Bamberger *et al*. (2005). Briefly, samples were incubated in 0.1 m phosphate buffer pH 7.8 (in a ratio 1:2 w/v) for 24 h at 4 °C, applying agitation during the first 40 min of incubation. Samples were subsequently centrifuged (1500 g, 15 min) and the supernatant fluid was collected.

Lincomycin determination

Lincomycin plasma and skin concentrations were determined by microbiological assay (Bennet *et al.* 1966) using *Kocuria rhizophila* (formerly *Micrococcus luteus*) ATCC 9341 as test microorganism. This method was selected because of its sensitivity, simplicity and good correlation with high-performance liquid chromatography (HPLC) determination (Strachunskii *et al.* 1993). Standard curves were prepared, depending on the sample matrix to be quantified, on normal cat plasma or phosphate buffer pH 7.8. Each sample was seeded in triplicate and each standard dilution in quintuplicate. The limits of detection and quantification of the method for plasma and phosphate buffer were 0.78 µg/mL and 1.56 µg/mL, respectively. The method was linear between 0.78 µg/mL and 50 µg/mL (r = 0.9965). Inter- and intra-assay coefficients of variation were less than 10%.

Pharmacokinetic analysis

Individual lincomycin plasma concentration–time curves were analysed by a non-compartmental approach with a software programme (PCNONLIN 4.0, SCI Software, Lexington, KY, USA). Major pharmacokinetic parameters were calculated according to classical equations (Gibaldi & Perrier 1982). The observed maximum plasma concentration (C_{max}) and time of maximum plasma concentration (T_{max}) were recorded directly from the data. The apparent terminal rate constant, k_z, was determined by linear regression of the last five or six points on the terminal phase of the logarithmic plasma concentration–time curves.

Statistical analysis

The means and standard deviations of pharmacokinetic parameters are expressed. Main pharmacokinetic parameters (area under the curve [$AUC_{(0-\infty)}$], elimination half-life [$T_{½}$] and mean residence time [MRT]), skin concentrations and skin: plasma concentration ratios were compared statistically for the two administration routes, applying a nonparametric paired test (Wilcoxon test). Differences were considered statistically significant at $p \leq 0.05$.

Susceptibility test on *Staphylococcus* spp. and *Streptococcus* spp.

A total of 31 *Staphylococcus* strains and 23 *Streptococcus* strains were isolated from skin and mucosal infections from clinical cases attending the Small Animals Hospital, Faculty of Veterinary Science, University of Buenos Aires.

Bacterial susceptibility to lincomycin was established by an antimicrobial disc diffusion test, using 2 µg clindamycin discs in accordance with CLSI (2008) recommendations. *Staphylococcus aureus* ATCC 25923 and *Streptococcus pneumoniae* ATCC 49619 were used as quality controls.

Results

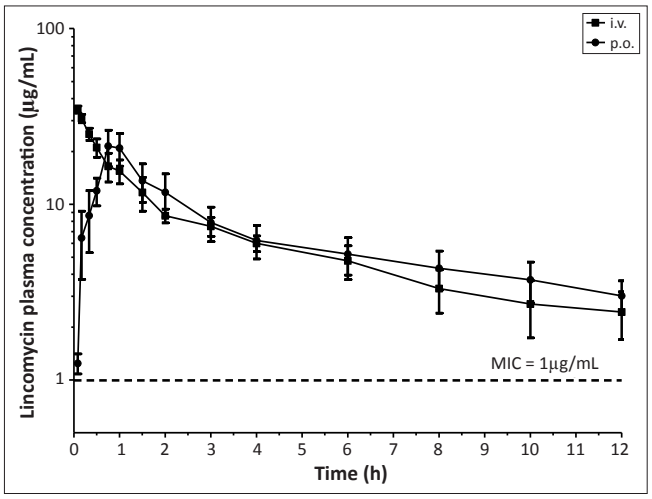
No adverse effects were observed during or following administration (either route) of lincomycin in any of the cats.

The mean plasma concentration–time curves for the two administration methods of the antibiotic are shown in Figure 1. Estimated pharmacokinetic parameters for both administration routes are summarised in Table 1.

Oral absorption was rapid (T_{max} = 0.80 h ± 0.11 h) although quite variable between animals (C_{max} = 22.52 µg/mL ± 10.97 µg/mL). Lincomycin oral bioavailability (F) was almost complete (F = 81.78% ± 24.05%). No statistically significant differences were observed between pharmacokinetic parameters after intravenous or oral administration.

Lincomycin skin concentrations are shown in Table 2. For both administration routes, the lincomycin concentrations were higher than the corresponding plasma concentration; skin: plasma ratio for intravenous and oral administration was 2.08 ± 0.47 and 1.84 ± 0.97, respectively. No statistically significant differences were observed in skin concentrations or skin: plasma ratios between administration routes.

Of the tested staphylococci samples, 87.09% (27/31) were susceptible to lincomycin, whilst 69.56% (16/23) of the tested streptococci samples were susceptible to the antibiotic.



Note: The MIC value corresponds to MIC50 (1 µg/mL) for *Staphylococcus* spp. and *Streptococcus* spp.
I.v., intravenous administration; MIC, minimum inhibitory concentration; p.o, oral administration

FIGURE 1: Mean (± SEM) lincomycin plasma concentration–time profile after intravenous and oral administration to cats at a dosing rate of 15 mg/kg (n = 5).

TABLE 1: Pharmacokinetic parameters (mean ± s.d.) of lincomycin after intravenous and oral administration to cats at a dosing rate of 15 mg/kg (n = 5).

Pharmacokinetic parameter	Intravenous administration	Oral administration
$C_{p(0)}$ (µg/mL)	38.84 ± 6.25	–
$AUC_{(0-\infty)}$ (µg.h/mL)	98.47 ± 40.83	97.92 ± 52.37
$V_{D(area)}$ (L/kg)	0.97 ± 0.15	–
T_{max} (h)	–	0.80 ± 0.11
C_{max} (µg/mL)	–	22.52 ± 10.97
Cl_B (L/h.kg)	0.17 ± 0.06	–
$T_{½}$ (h)	4.20 ± 1.12	4.12 ± 1.44
MRT (h)	5.50 ± 1.64	6.38 ± 2.22
F (%)	–	81.78 ± 24.05

Note: No statistically significant differences were observed between the two routes of administration.
$AUC_{(0-\infty)}$, area under the plasma concentration–time curve from 0 to infinity; C_{max}, maximum concentration; $C_{p(0)}$, plasma concentration at 0 time; Cl_B, body clearance; F, bioavailability; MRT, mean residence time; T_{max}, time of maximum concentration; $T_{½}$, elimination half-life; $V_{D(area)}$, volume of distribution

TABLE 2: Lincomycin plasma and skin concentrations (mean ± s.d.) taken two hours after lincomycin administration and skin: plasma concentration ratio after intravenous and oral administration (15 mg/kg) to cats (n = 5).

Tissue concentration	Intravenous administration	Oral administration
Plasma (µg/mL)	8.60 ± 1.73	11.70 ± 7.18
Skin (µg/g)	17.26 ± 1.32	16.58 ± 0.90
Skin: plasma ratio	2.08 ± 0.47	1.84 ± 0.97

Discussion

Lincomycin is an antibiotic with long duration in the body owing to its lipid solubility and wide tissue distribution. It has good activity against Gram-positive cocci and anaerobes. Because of these features, lincomycin is recommended for the treatment of a variety of skin, respiratory, gastrointestinal, soft-tissue and bone infections (Greene & Boothe 2012; Patel 2006).

The microbiological assay for measuring lincomycin concentrations in plasma and other biological matrices has been used in many studies (Abo El-Sooud *et al.* 2004; Albarellos *et al.* 2011; Brown *et al.* 1975; Burrows *et al.* 1986; Marcus, Ziv & Glickman 1995; Nielsen & Gyrd-Hansen 1998; Soback *et al.* 1987; Ziv & Sulman 1973). This analytical method is appropriate and accurate as lincomycin has no active metabolites (Brown *et al.* 1975; Brush *et al.* 1976; Hornish *et al.* 1987).

It is important to emphasise that animals were anaesthetised for skin sampling for approximately 30 min. Clinical parameters were carefully monitored throughout the procedures and all the cats remained stable, but haemodynamic modifications influencing the pharmacokinetic behaviour of lincomycin cannot be ruled out. However, previous antimicrobial pharmacokinetic studies performed in anaesthetised dogs, although with a different antibiotic, showed no significant changes in pharmacokinetic parameters (Duval & Budsberg 1995).

Lincomycin pharmacokinetic parameters after intravenous administration were similar to those reported in a previous study (Albarellos *et al.* 2012). However, the dose used in the present study was higher than the one used in the earlier study by Albarellos *et al.* (2012). This difference is clearly observed in the dose-dependent parameters that varied accordingly.

Lincomycin oral absorption was rapid and almost complete (T_{max} = 0.80 h and F = 81.78%). Similar high oral bioavailability was reported by Nielsen and Gyrd-Hansen (1998) after lincomycin administration to fasted pigs.

No statistically significant differences were observed for elimination-related parameters ($T_{½}$ and MRT) when comparing the two administration routes.

Lincosamides are lipophilic antibiotics and are therefore expected to achieve higher concentrations in most tissues than in plasma (Giguère 2006). In a study analysing clindamycin

tissue concentrations in cats, Brown *et al*. (1990) found tissue: plasma ratios > 1. In the present study we found similar results. Lincomycin skin concentrations were higher than the corresponding plasma concentrations and skin: plasma ratios were also > 1, reflecting lincomycin accumulation in this tissue. However, it was noted that whole tissue concentrations are difficult to interpret because they represent the sum of all concentrations (intracellular, extracellular fluid and also any remaining blood contamination). It is also important to note that in the present study skin samples were taken at a single time point (2 h after antibiotic administration) and a single dose was administered. Therefore, the expected tissue accumulation in an ordinary therapeutic treatment could not be analysed.

Lincomycin skin concentrations and skin: plasma ratios were equivalent for both administration routes assayed. This finding is in accordance with the similar plasma concentration profile of the drug for the two administration routes and its high oral bioavailability.

Plasma lincomycin concentrations after intravenous or oral administration were well above MIC_{50} values recorded in literature (Albarellos *et al.* 2012; Giguère 2006) for the entire proposed dosing interval for this antibiotic (8 h – 12 h) (Plumb 2011). According to results of this study, a 15 mg/kg oral dose of lincomycin could allow a 12 h dosing interval in cats.

Similarly, lincomicyn skin concentrations were above an MIC_{50} of 1 μg/mL, but this refers to a single time point. However, it is possible to assume that lincomycin accumulates in tissues (because of its chemical characteristics) and therefore tissue concentrations will remain above plasma concentrations throughout the dosing interval.

Most of the staphylococci and streptococci samples tested in this study were susceptible to lincosamides (87.09% and 69.56%, respectively); however, it is important to consider that lincomycin antibacterial activity could be overestimated because antimicrobial susceptibility was evaluated with clindamycin discs (a more potent lincosamide) (CLSI 2008). Nevertheless, bacterial susceptibility rates for lincomycin found in this study suggest that lincomycin could be a good first option for treating the majority of skin infections in cats.

Conclusion

According to the data obtained in this study, lincomycin would be a useful alternative for the treatment of uncomplicated skin infections in cats.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

G.A.A. (University of Buenos Aires) and M.F.L. (University of La Plata) were the project leaders and responsible for experimental and project design. L.M. (University of Buenos Aires) and S.M.P. (University of Buenos Aires) performed most of the experimental *in vivo* work. G.A.A.D. (University of Buenos Aires) performed most of the bacteriological work.

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