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STANDARD ARTICLE

Pharmacokinetics of meloxicam after oral administration of a granule formulation to healthy horses

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Background: Nonsteroidal anti-inflammatory drugs are administered in horses for several systemic diseases. Selective cyclooxygenase-2 inhibitors are preferred because of lower risk of adverse effects. Several meloxicam formulations have been tested in horses, but a recently marketed granule oral formulation has not been studied.

Objective: To characterize the pharmacokinetics of a novel granule meloxicam formulation in fasted and fed horses, and to compare pharmacokinetic features with oral suspension and tablets.

Animals: Seven healthy adult horses.

Methods: Meloxicam was administered at 0.6 mg/kg in fasted or fed horses. Blood samples were collected for pharmacokinetic analysis, and vital signs, hematology, and biochemistry variables were monitored for 72 hours.

Results: No adverse effects were detected. Volume of distribution and clearance after intravenous administration of meloxicam were 0.36 L/kg and 29.12 mL/h/kg, respectively, with a 12.39 hours of terminal half-life. Protein binding was of 97%. Bioavailability was high for every oral formulation, ranging 70%-110%, without feed effect. Because of a slower absorption, meloxicam after administration of granules had a longer half-life (24 and 34 hours, fasted and fed, respectively) and mean residence time (31 and 47 hours), than suspension and tablets (ranging 10-13 and 13-15 hours, respectively). In addition, the time above therapeutic concentration was higher for the granule formulation than other formulations.

Conclusions and Clinical Importance: Granule formulation has different PK parameters compared to other oral formulations, which could enable this formulation to be used for different dosage regimens in order to reach a desired clinical effect or decrease the risk of adverse effects.

KEYWORDS

equids, granule oral formulation, pharmacology, selective COX-2 inhibitors

1 | INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are 1 of the most commonly used drugs in veterinary practice because of their anti-inflammatory, analgesic, and antipyretic effects. In equine medicine, these compounds are prescribed for postoperative management and systemic disturbances such as pleuropneumonia, colic, or neurologic diseases, but are mainly administered for musculoskeletal disease and pain relief.[1–4]

Despite their broad use in clinical practice, nonselective COX inhibitors (ie, flunixin meglumine, phenylbutazone, and ketoprofen) are associated to adverse effects such as colitis, renal damage, or gastric ulcers, especially in hypovolemic and dehydrated animals or as a species-specific or individual predisposition.[2,4,5] In order to avoid the aforementioned adverse effects, agents that selectively inhibit the COX-2 isoform (mainly meloxicam, carprofen, and firocoxib) have been proposed as safer and more effective alternatives in horses.[3,4,6,7]

Meloxicam is administered mainly to treat inflammatory conditions, particularly orthopedic disorders, or as a pain relief owing to colic, trauma, or in postoperative support.[2,3,8] Several formulations are marketed for equids both adults and foals in Europe, Australia, and

Abbreviations: AUC, area under concentration-time curve; AUMC, area under moment-curve; Cl, clearance; HPLC, high-performance liquid chromatography; MAT, mean absorption time; MRT, mean residence time; NSAID, nonsteroidal anti-inflammatory drug; PK, pharmacokinetic; TS, total solids.

New Zealand.[9] At this time, pharmacokinetic (PK) studies in healthy and postoperative animals have been only reported for intravenous and oral routes, specifically suspension and tablets (off-label use) formulations.[9–18] On the other hand, PK parameters of a granule oral formulation, which is used in equine practice in Europe, Australia, and New Zealand, have not been evaluated. This novel formulation would allow an easier administration compared to other oral formulations (suspension and tablets) and could support a different regimen dose in those instances where actual dose recommendations appear to be less effective.

Therefore, the objectives of this study were (*a*) to characterize the PKs of a granule meloxicam oral formulation in healthy adult horses; (*b*) to evaluate the effect of fasting and feeding on PKs parameters; and (*c*) to compare this novel marketed formulation with tablets and oral suspension.

2 | MATERIAL AND METHODS

2.1 | Animals

Seven healthy horses, 6 nonpregnant females and 1 gelding, weighing 451 (122) kg and 8 (9.2) years old, housed on the same farm, were used in this study. All animals were similarly managed, with free access to water and a similar daily diet (4 kg of commercial grain and approximately 8-9 kg of straw divided in 2 meals). The diet composition was the following: protein 19%, fat 3%, sugar 7%, starch 22%, fiber 13%, and ash 8%.

All animals were considered healthy based on clinical history and physical examination, hematology, and serum biochemistry. No treatments had been administered at least 2 months before the study.

This study received approval from both the Welfare Committee of Animal Experimentation from the University of Cordoba (2016PI/17) and the Rural Development, Fishing and Agriculture Ministry of Junta de Andalucia (21-10-2016-165). Animals were handled according to national guidelines for research animals.

2.2 | Experimental protocol design

The meloxicam formulations tested were: granule (Inflacam granule 330 mg/sachet, Virbac, Carros, France), suspension (Inflacam suspension 1.5 mg/mL, Virbac, Carros, France), and tablets (Meloxicam tablets 15 mg/tab, Stada, Barcelona, Spain). Meloxicam formulations were administered by nasogastric tube diluted in 1 L of water, being tablets previously crushed.

All animals received a single dose of meloxicam at 0.6 mg/kg early in the morning (7-9 AM). Each oral formulation was tested in fasted (feed was removed at 6-7 PM of the night before) and fed horses (animals were fed 1.5-2 hours before the test). Four hours after drug administration, horses were returned to their boxes and water (automatic drinker) and food access were regained. A randomized cross-blinded study was carried out, with a 2 weeks washout period between experiments.

In order to determine the bioavailability of oral formulations of meloxicam, a single dose of meloxicam (Loxicom, Norbrook Laboratories Limited, Newry, Ireland) was administered IV at 0.6 mg/kg.

Jugular vein catheters were aseptically placed the day before each experiment and lines were flushed with heparinized solution during the experiments. Blood samples (8 mL) for PK analyses were collected into plain tubes at the following times: 0, 1, 5, 10, 15, 30, 45, 60, 90, 120, 240, and 360 minutes, and 12, 24, 36, 48, and 72 hours.

In order to assess any potential drug adverse effects, a physical examination was performed including heart rate, respiratory rate, body temperature, gut motility, digital pulse, mucous membrane color, and refill capillary time at the same time points as mentioned above. In addition, blood samples were collected into EDTA (2 mL) and heparin (4 mL) tubes at baseline, 6, 12, 24, 36, 48, and 72 hours for hematology and biochemistry (total solids [TS], albumin, fibrinogen, creatinine, urea, aspartate transaminase, gamma-glutamyl transferase, and total bilirubin concentrations). Hematological variables were assessed by an automatic analyzer (ProCyte, Idexx Laboratories, Hoofddorp, the Netherlands), TS were measured by refractometry, fibrinogen by heat-denaturation method, and the rest of biochemical variables by spectrophotometry (Biosystems A15, Biosystems, Barcelona, Spain).

2.3 | High-performance liquid chromatography (HPLC) method, protein binding assay, and PK analysis

Serum concentrations of meloxicam were measured by a modified HPLC method previously reported.[13] A 500 μL of horse serum was spiked with 50 μL of standard internal solution of piroxicam; then, 200 mg of NaCl were added and mixed with 500 μL of acetonitrile. The mixture was vortex-mixed for 5 minutes and centrifuged at 28 300*g* for 15 minutes at 4°C. The upper organic layer was extracted and 50 μL were injected into the chromatographic system.

The separation and detection were performed using a HPLC system with diode array detection, with a Supelcosil LC18 (250 × 4.6 mm, 5 μm) column, with an isocratic mobile phase of 65% acetonitrile and 35% buffer (20 mM KH_2PO_4 at pH 3.5) at 1 mL/min. Under these conditions, piroxicam and meloxicam were eluted at 5.5 and 7.7 minutes approximately. The detection was performed at 355 nm.

Quality controls were prepared from a pool of blank horse serum spiked with 7 meloxicam concentrations (between 0.10 and 10 μg/mL). Calibrations were obtained by linear regression of meloxicam and piroxicam areas versus known concentrations. Each point was established from an average of 5 determinations. Correlations coefficients (*r*) were >0.99 for calibration lines. The percentage recovery was determined by comparing the peak areas of serum samples spiked with different amounts of drug and treated as any samples with the peak areas of the same standards prepared in phosphate buffer. Each point was established from an average of 5 determinations. The mean percentage recovery of meloxicam was 87.23%. The assay precision (R.S.D.) was assessed by expressing the SD of repeated measurements as a percentage of the mean values. Serum intra-day precision was estimated from 9 replicates of 3 standard samples used for calibration lines (R.S.D. < 6.61%). Inter-day precision was estimated from the analysis of standard spiked samples on 3 separate days (R.S.D. < 7.83%). The limits of quantification and detection were 0.05 and 0.025 μg/mL, respectively.

Protein binding assay was determined by in vitro equilibrium dialysis using blank serum samples from horses and sodium phosphate buffer at 64 mM adjusted at pH 7.4. Meloxicam concentrations of 0.5, 1.0, 2.5, 5, and 10 μg/mL were used. After dialysis, samples were collected and measured by HPLC method as described

above. The unbound fraction f_u was estimated as the ratio of concentration determined in the buffer respect to serum.

Serum meloxicam time-concentration data were analyzed by a noncompartmental analysis because, as it has been previously described, this independent model approximation is more accurate to determine parameters as mean absorption time, bioavailability, and elimination half-life after oral administration of a drug without the model assumption, and it is a common part of PK analysis in intensive-sampled clinical studies.[19,20] Moreover, this approach has fewer assumptions than model-based approaches. The software selected was the ncappc package implemented in RStudio with R software version 3.2.5.[19] Specifically, this package is a versatile tool that successfully estimates PK parameters and satisfactorily has been previously validated with other PK software.[19]

The following parameters were calculated: the maximum concentration (C_{max}) and the time to reach C_{max} (T_{max}) were taken directly from oral data; serum concentration-time data were log-normally distributed and the elimination rate constant (λ_Z) was estimated by linear regression of time versus log concentration data; the elimination half-life as $t_{1/2}\lambda_z = (\ln 2)/\lambda_Z$; area under the concentration-time curve (AUC) and area under moment-curve (AUMC) were calculated by using the linear trapezoidal method with extrapolation to time infinity; the mean residence time (MRT) was calculated as AUMC/AUC; the mean absorption time (MAT) was calculated as $MRT_{PO} - MRT_{IV}$; systemic clearance (Cl) was estimated as dose/AUC; apparent volume of distribution at steady state (V_{ss}) was calculated as dose AUMC/AUC^2; and bioavailability (F%) was calculated by the method of corresponding areas as $(AUC_{PO} \times dose_{IV}) \times 100/(AUC_{IV} \times dose_{PO})$.

After PK analysis, serum concentration-time curves, obtained for each route, formulation, and feeding status, were graphically overlapped with the effective meloxicam concentrations in horses previously reported with object to assess the time above these concentrations throughout the dose interval.[12,21]

2.4 | Statistical analysis

Normality was assessed by the Kolmogorov-Smirnov test. Pharmacokinetic data, vital signs, and hematological and biochemical results were non-normally distributed, thus results are expressed as medians and interquartile ranges (25th percentile - 75th percentile). Percentiles were calculated by the Tukey's hinges test. Friedman's test was used to determine differences over time, followed by the Wilcoxon's test to further assess time differences. In addition, a Kruskal-Wallis test was performed in order to study differences between oral formulations and between fasted and fed horses. $P < .05$ was considered statistically significant. Statistical analysis and figures were performed by SigmaPlot software for Windows version 11.0 (Systat Software Inc, San Jose, California).

TABLE 1 Pharmacokinetic parameters of intravenous (IV) and different oral meloxicam formulations (granule, suspension, and tablets) after a single 0.6 mg/kg dose in fasted and fed horses (n = 7)

Parameter	IV	Granule		Suspension		Tablets	
	Fasted	Fasted	Fed	Fasted	Fed	Fasted	Fed
λ_z (L/h)	0.06 (0.02)	0.03 (0.00)[a,d]	0.02 (0.02)[a]	0.05 (0.03)	0.06 (0.03)	0.07 (0.03)	0.06 (0.04)
	(0.04-0.08)	(0.02-0.03)	(0.01-0.04)	(0.05-0.10)	(0.04-0.08)	(0.04-0.09)	(0.04-0.08)
$t_{1/2}\lambda_z$ (h)	12.39 (4.07)	24.20 (3.73)[a,d]	34.08 (20.76)[a]	13.17 (5.25)	10.85 (6.31)	10.33 (5.40)	12.33 (7.87)
	(8.82-16.07)	(21.50-44.66)	(16.44-56.69)	(7.19-14.86)	(8.46-17.74)	(7.97-16.25)	(8.72-17.45)
T_{max} (h)	-	1.5 (1.00)[c]	1.00 (0.25)	1.00 (0.50)[c]	0.50 (0.25)	1.50 (0.00)[c]	0.75 (0.00)
		(1.00-2.00)	(0.75-1.50)	(0.75-2.00)	(0.50-1.00)	(1.00-2.00)	(0.50-1.50)
C_{max} (μg/mL)	-	1.21 (0.32)[a]	0.85 (0.35)[a]	2.08 (0.64)	2.10 (0.84)	1.98 (1.11)	2.70 (1.48)
		(0.76-1.68)	(0.74-1.46)	(1.55-2.38)	(1.59-2.59)	(1.02-3.43)	(1.31-3.26)
AUC_0^{∞} (μg/mL*h)	20.61 (4.47)	20.27 (9.86)[b]	20.60 (6.17)[a]	17.89 (1.46)	15.42 (3.33)	15.60 (2.25)	18.26 (6.60)
	(16.02-23.51)	(16.65-28.38)	(15.05-26.77)	(14.22-20.90)	(12.94-21.98)	(11.46-23.77)	(9.54-20.06)
MRT (h)	11.82 (2.29)	31.57 (1.92)[a,d]	47.55 (25.29)[a]	14.58 (5.78)	13.76 (2.95)	14.01 (5.28)	14.82 (2.27)
	(9.72-14.85)	(26.47-59.39)	(24.06-77.10)	(10.17-18.82)	(11.77-20.91)	(11.06-19.36)	(11.25-17.61)
MAT (h)	-	21.07 (6.85)[a]	36.46 (20.87)[a]	4.16 (5.35)	2.02 (3.59)	3.01 (6.01)	2.12 (4.15)
		(13.84-49.67)	(11.43-67.39)	(−2.55-6.87)	(−0.05-8.19)	(−1.94-7.68)	(−0.76-6.49)
F (%)	-	110.37 (25.84)[a]	96.55 (46.94)	88.27 (12.81)	75.43 (40.30)	78.13 (36.95)	90.11 (18.63)
		(83.50-131.29)	(64.00-138.73)	(71.13-105.56)	(65.56-110.34)	(53.73-119.22)	(40.56-106.48)
V_{ss} (L/kg)	0.36 (0.21)	-	-	-	-	-	-
	(0.27-0.57)						
Cl (mL/h/kg)	29.12 (7.23)	-	-	-	-	-	-
	(25.52-37.45)						

Data are expressed as median, interquartile ranges (IQR) and ranges (bottom line).
Abbreviations: λ_z, elimination rate constant; AUC_0^{∞}, area under the serum concentration-time curve; Cl, total body clearance; F (%), bioavailability; MAT, mean absorption time; MRT, mean residence time; C_{max}, maximum meloxicam serum concentration; $t_{1/2}\lambda_z$, terminal half-life; T_{max}, time to reach maximum serum concentration; V_{ss}, apparent volume of distribution at steady state.
[a]$P < .05$ versus oral suspension and tablets in fasted and fed horses, respectively.
[b]$P < .05$ versus tablets in fasted horses.
[c]$P < .05$ versus respective fed horses.
[d]$P < .05$ versus IV.

3 | RESULTS

No adverse effects were noted and horses remained normal throughout the experiments. Hematology and biochemistry variables remained within normal ranges (Supporting Information Table S1).

Pharmacokinetic parameters are presented in Table 1 and concentration-time curves of meloxicam for each route, formulation, and feeding status are plotted in Figures 1 and 2, respectively.

Serum concentrations of meloxicam after IV administration rapidly declined during the first 6 hours with a second slower elimination from 6 to 36 hours (Figure 1A). The terminal half-life and MRT values were 12.39 (4.07) and 11.82 (2.29) hours, respectively. AUC_0^{∞}, Cl, and V_{ss} were 20.61 (4.47) μg/mL/h, 29.12 (7.23) mL/h/kg, and 0.36 (0.21) L/kg, respectively (Table 1). Meloxicam protein binding was high, reaching a value close to 97.75 (2.72)%.

Oral bioavailability was high for each oral formulation (ranging between 75 and 110%), however granule reached higher ($P < .05$) F values than the other formulations (Table 1). Regardless of its higher oral bioavailability, granule presented lower C_{max} concentrations than suspension and tablets both in fasting ($P = .03$ and .004, respectively) and fed ($P = .02$ and .02, respectively) horses respectively (Figure 1B, C). In contrast, granule had significantly (8-16-folds) longer MAT than suspension and tablet formulations both in fasting ($P = .004$ and .002, respectively) and feeding ($P = .004$ and .004, respectively) (Table 1). In addition, MAT granule showed a 2-fold longer ($P < .05$) half-life and MRT than suspension and tablets both in fasting and fed horses. These findings suggest that the composition or structure of the granule formulation could have caused a reduction in the meloxicam absorption rate, thus affecting the elimination rate (λ_z) and MRT in this formulation (Table 1).

Although feeding status did not significantly affect to PK results for the formulations tested (Figure 2), T_{max} was faster in fed horses in each formulation (Table 1).

4 | DISCUSSION

Meloxicam is used in equids in Europe, Australia, and New Zealand or under an extra-label or compounded use in other countries such as United States, but the PK characteristics for a novel granule formulation have not been studied at this moment. Pharmacokinetics results of this study on healthy horses demonstrate that meloxicam granule formulation has an excellent bioavailability, with longer MAT, half-life, and MRT than other oral formulations such as suspension and tablets without influence of feeding status. These properties allow a slower elimination rate and a longer maintenance of an effective plasmatic concentration in granule formulation compared to the other formulations.

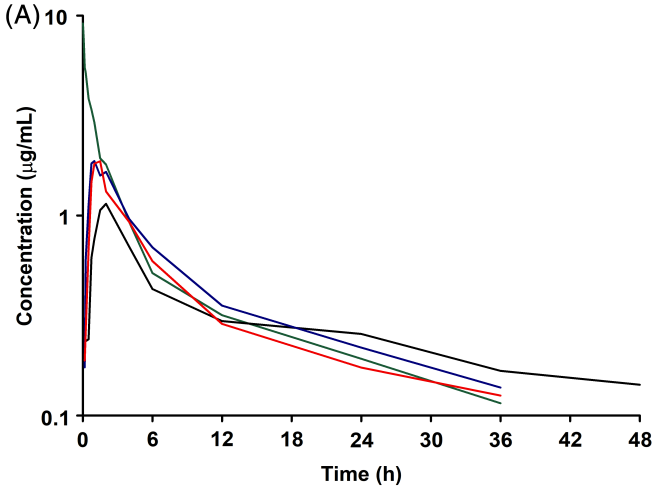
Pharmacokinetic results for the intravenous formulation were similar to those reported previously.[11,13,18] Protein binding analysis yielded that meloxicam was highly bound to plasma proteins. Similar results have been reported in dogs, humans, rats and, mini-pigs.[22]

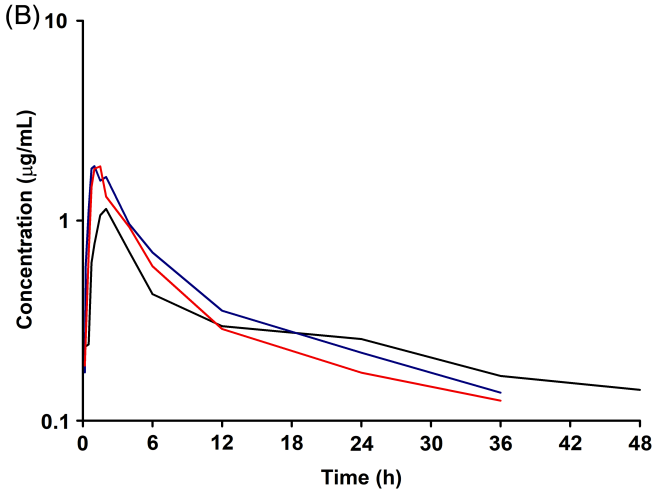
In our study, feeding status did not influence on PK results for any of meloxicam formulations, therefore granule formulation could be administered at any time of the day without loss of efficacy. Our results yielded a faster T_{max} values in fed horses compared to fasted ones. In contrast, a previous study using an oral suspension formulation reported a slower absorption in fed horses compared to fasted ones.[11] This discrepancy can be attributable to differences in the experimental design, because we administered the drugs through nasogastric tube between 1.5 and 2 hours after feeding, whereas in the mentioned study meloxicam was mixed with wheat bran and PO provided as a mash. A possible explanation is the fact that the absorption of some drugs in fed horses can be enhanced with smaller meals, whereas higher amounts ingested can produce the opposite.[22] In addition, the physiologic status of the gastrointestinal tract could have modified the absorption rate of meloxicam, but the fraction absorbed remained unchanged as high oral bioavailability was achieved.[12]

Although granule formulation reached a lower C_{max} than suspension and tablet, serum meloxicam concentrations were detected longer (48 hours) than in the other formulations. These findings highlight that granule formulation has different properties that allow a slower intestinal absorption, prolonging the half-life and increasing the MRT, being necessary long-term administration studies in order to evaluate the possible toxicity. These results also suggest that the slower elimination of granule meloxicam was mainly caused by its slower absorption, as proved by the $t_{1/2}\lambda_z$ and MRT observed in this study, discarding an effect of lower clearance. In comparison with the PK data previously reported for meloxicam in horses, discrepancies can be observed (Table 2), with granule PK results being different than those reported by Toutain et al but similar to those reported by other authors.[9,15,16] Compared to suspension and tablets formulations, PK results in this study were different to some described previously.[9,15,16] These differences could be attributable to interindividual variability in meloxicam intestinal absorption because of intestinal motility or variations in the experimental design, that is, drug administered as a mash mixed with molasses versus after feeding, administration through nasogastric intubation versus PO, drug preparation (ie, tablet crushed versus in suspension), etc.[9,23] In addition, other factors such as breed, assay sensitivity, stressors, time-point sampling, or sample size cannot be discarded.[24]

If results from our study are compared with previous pharmacodynamic reports, serum concentrations for meloxicam granule formulation remained above the therapeutic range reported in an experimental model of induced arthritis,[12] either for 0.5 or 1 mg/kg of meloxicam dose IV, for a longer time than suspension and tablet formulations (Figure 3). According to the efficacy concentrations reported by Toutain and Cester for the variables stride length and clinical lameness scores, granule formulation in our study inhibited COX-2 enzyme for a longer time (12 hours) than tablet and suspension formulations. On the other hand, if results are compared with in vitro data,[21] serum concentrations of the granule formulation remained higher than the therapeutic range by 24 hours, whereas suspension and tablet formulations fell below this range approximately at 18 hours post-administration (Figure 3). However, it has been demonstrated that COX selectivity cannot be accurately predicted by in vitro studies.[25]

Pharmacokinetic characteristics of the granule formulation turn this equine marketed product into an excellent option for treatments where long-term administration is compelling. In addition, because of its prolonged MRT and longer maintained serum therapeutic concentrations, a single daily regimen dose administration is feasible in contrast to





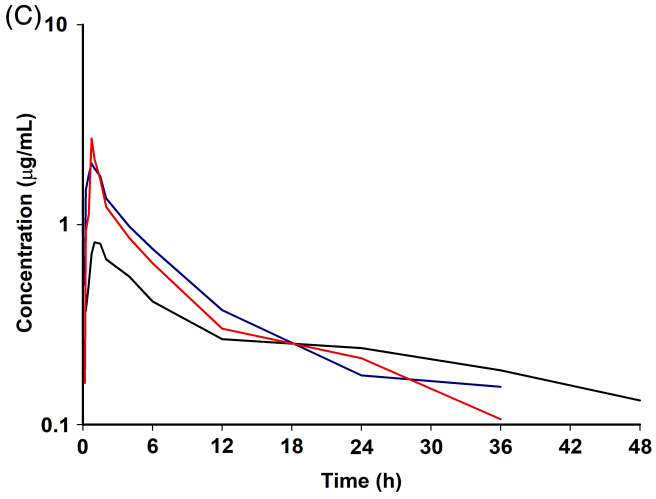
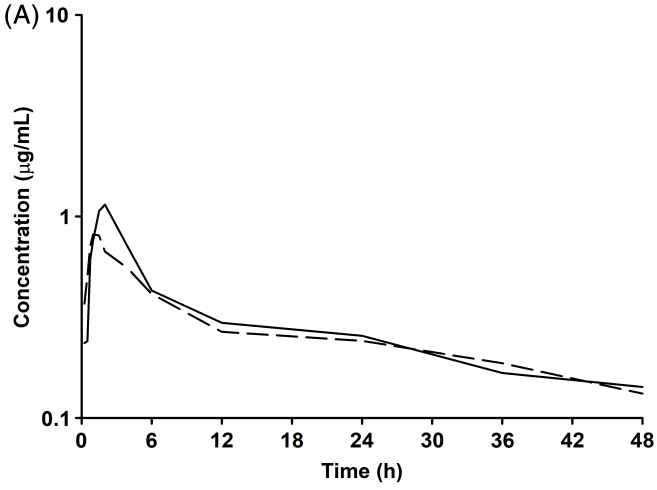
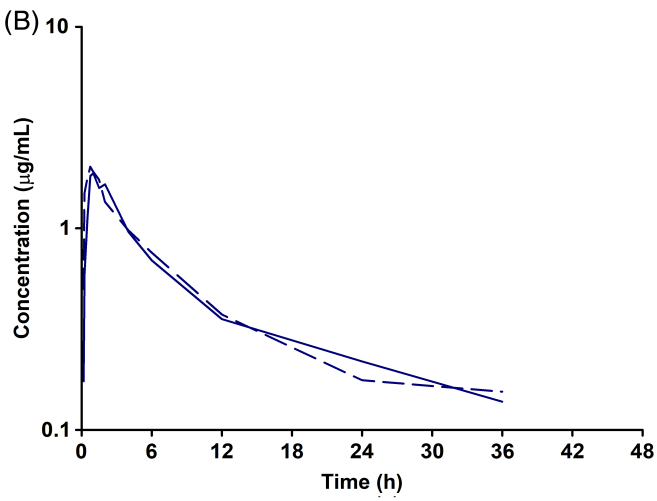


FIGURE 1 Semilogarithmic plot of serum meloxicam concentrations after a single dose (0.6 mg/kg) in 7 healthy horses. A, Concentrations for intravenous (green line) versus granule (black line), suspension (blue line), and tablet (red line) formulation in fasted horses; B, concentrations for oral formulations in fasted horses; and C, concentrations for oral formulations in fed horses. Plots are expressed as median values





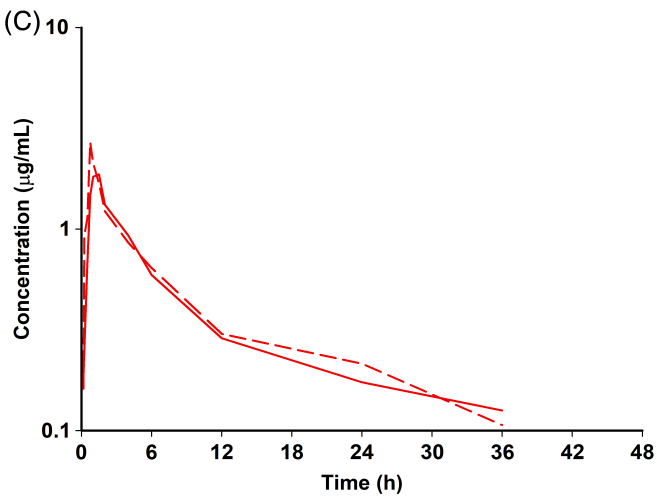


FIGURE 2 Semilogarithmic plot of serum meloxicam concentrations after a single dose (0.6 mg/kg) in 7 healthy horses. A, Granule formulation in fasted (black continuous line) and fed (black dashed line) horses; B, suspension formulation in fasted (blue continuous line) and fed (blue dashed line) horses; and C, tablet formulation in fasted (red continuous line) and fed horses (red dashed line). Plots are expressed as median values

other commonly used oral NSAIDs.[26–28] Moreover, the dose of the following day could be administered later during the day.

At this moment, meloxicam (Metacam, Boehringer Ingelheim) is listed on Federation Equestre Internationale detection list with a 3-day detection time.[29] Despite that granule formulation having a prolonged MRT and half-life, meloxicam was not detected in blood for longer than 48 hours. Urine or tissue detection times have not been established for meloxicam granule formulation, therefore complementary studies are warranted.

TABLE 2 Comparison of previous studies reporting meloxicam pharmacokinetic parameters in healthy horses after an oral single dose at 0.6 mg/kg

Reference	11		15	9		16	17
Formulation	**Suspension**	**Suspension**	**Suspension**	**Suspension**	**Tablets**	**Tablets**	**Suspension**
Population	Adults	Adults	Adults	Adults	Adults	Adults	Foals
Sample size	6 or 8	8	16	8	8	7	10
Feeding status	Fed	Fasted	Fed	Fasted	Fasted	Fed	Nursing
Administration	PO, just before fed, mixed with wheat bran mash	Oral directly	Oral directly	Oral directly	Oral mixed with molasses	PO, 1 hour after fed, mixed with molasses	Oral directly
$t_{1/2}\lambda_z$ (h)	7.7 ± 2.0	N.R.	10.2 ± 3.0	6.4 ± 3.0	6.5 ± 2.8	5.2 ± 1.4	2.5 ± 0.2
T_{max} (h)	3.4 ± 1.2	1.5 ± 1.1	2.6 ± 1.9	5.5 ± 4.1	2.5 ± 0.8	3.5 ± 3.3	<1.5
C_{max} (μg/mL)	1.7 ± 0.6	2.6 ± 0.6	0.9 ± 0.1	0.7 ± 0.2	0.7 ± 0.2	1.6 ± 0.7	1
AUC_0^{∞} (μg/mL*h)	N.R.	N.R.	11.3 ± 3.2	9.3 ± 2.6	8.4 ± 2.8	11.2 ± 2.0	N.R.
MRT (h)	9.3 ± 1.6	7.22 ± 1.7	N.R.	11.1 ± 1.6	9.6 ± 1.3	7.2 ± 1.4	N.R.
MAT (h)	5.7 ± 1.8	3.6 ± 1.4	N.D.	N.D.	N.D.	N.D.	N.R.
F (%)	96.0 ± 13.2	85.3 ± 19.4	N.D.	N.D.	N.D.	N.D.	85-98

Data are expressed as mean ± SD.
Abbreviations: AUC_0^{∞}, area under the serum concentration-time curve; C_{max}, maximum meloxicam serum concentration; *F* (%), bioavailability; MAT, mean absorption time; MRT, mean residence time; N.D., non determined; N.R., non reported; $t_{1/2}\lambda_z$, terminal half-life; T_{max}, time to reach maximum serum concentration.

It has been demonstrated that foals and donkeys have a higher meloxicam clearance than adult horses and, therefore, a shorter MRT, being necessary a shorter interval dose.[13,17] Although more studies are necessary, meloxicam granule formulation could be recommended for foals and donkeys, because its PK characteristics could ameliorate these age and species-associated idiosyncrasies.

If meloxicam PK parameters from our study are compared to other COX-2 selective NSAIDs marketed for equids such as firocoxib, similar findings are observed. Although meloxicam is not an approved drug by the Food and Drug Administration at this moment (but accepted by the European Medicines Agency), it has been demonstrated both in vivo and in vitro that it has a higher selectivity for COX-2 isoform compared to other common NSAIDs drugs.[30,31] Both drugs have high MRT, oral bioavailability, and half-life both in intravenous and oral formulations.[24,32,33] Noteworthy, differences between tablets and paste formulations were not observed in 1 of them.[24] Despite meloxicam tablets administration being a common off-label practice among horse owners, results from this study demonstrate that this formulation had different PK results than other marketed products, with lower oral bioavailability and half-life, and faster elimination rate, although non adverse effects have been detected in a previous study.[16]

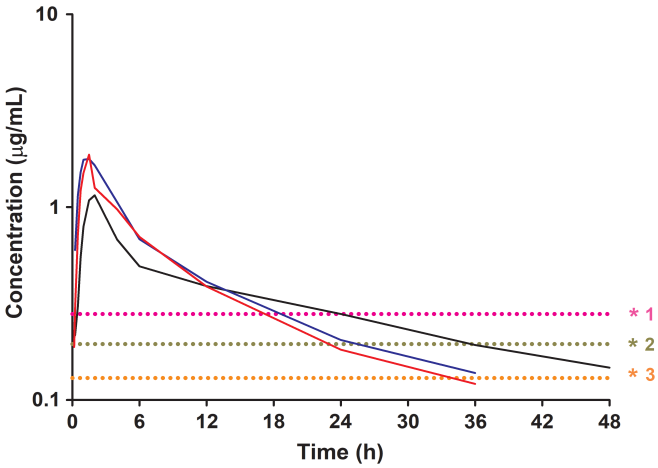


FIGURE 3 Semilogarithmic plot of serum meloxicam concentrations in 7 healthy fasted horses after a single dose (0.6 mg/kg) of granule (black line), suspension (blue line), and tablet (red line) formulation. Dotted lines represent the effective concentrations previously reported. *[1] COX-2 inhibition concentration (0.27 μg/mL) reported by Beretta et al; *[2] effective concentration for improvement in lameness score (0.19 μg/mL) reported by Toutain and Cester; *[3] effective concentration for improvement in stride length (0.13 μg/mL) by Toutain and Cester. Plots are expressed as mean values

5 | CONCLUSIONS

Pharmacokinetic results of the meloxicam granule formulation at 0.6 mg/kg dose demonstrate that this novel marketed equine drug has good oral bioavailability, reaching effective serum concentrations by 48 hours, without feeding status influence.

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CONFLICT OF INTEREST DECLARATION

None of the authors has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this study. The authors would like to emphasize that both experimental trial and results analysis were not biased or manipulated by Virbac S.L.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

This study received approval from both the Welfare Committee of Animal Experimentation of the University of Cordoba (2016PI/17) and the Rural Development, Fishing and Agriculture Ministry of Junta de Andalucia (21-10-2016-165). Animals were handled according to national guidelines for research animals.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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