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Original manuscript

Pharmacokinetics of meloxicam in lactating goats (*Capra hircus*) and its quantification in milk after a single intravenous and intramuscular injection.

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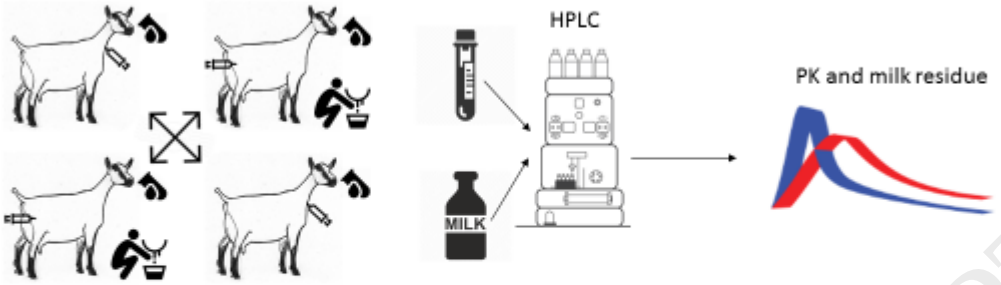
Graphical abstract



Highlights

- The intravenous and intramuscular administration of MEL in lactating goats showed a similar pharmacokinetic profile.
- The IM bioavailability was complete
- In silico simulation showed plasma concentration above the therapeutic plasma concentrations determined for other animal species
- MEL depletion in milk shown to be in line with that reported for cattle.

Abstract

Domestic goats, although present in large numbers worldwide, are still considered a minor species in Europe and the USA. Due to their minor status, new therapies directed to relieve pain is a neglected area of investigation. Unfortunately there is a lack of approved drugs for this species and many drugs are administered in an extra-label manner. Often no information on the safety profile for goats and

for humans consuming their products is available. Meloxicam (MEL) is a potent anti-inflammatory drug characterized by a preferential COX-2 isoenzyme inhibition. The aim of this study was to determine the pharmacokinetics of MEL at the dose of 0.5 mg/kg in lactating goats after intravenous (IV) and intramuscular (IM) administration and to quantify its residues in milk. The analytical method was performed by the HPLC diode array detector. The IV and IM administrations of MEL in lactating goats showed suitable pharmacokinetic profiles for this animal species. The IM route showed a bioavailability of 105% and long half-life of elimination (10.82 hr). The simulation of multiple daily IM injections provides a plasma concentration above the therapeutic concentrations determined for other species for the majority of 24 hr. The high IM bioavailability, the long half-life of elimination and the mean plasma concentration at the steady state suggested that once a day administration might be sufficient. MEL residues were quantifiable in milk up to 48 hr in IM group and 60 hr in IV group. These data seems to be in line with the milk depletion reported in cattle. Further studies are necessary to establish if the minimal effective concentration determined in other animal species can be applied to goats too.

Keywords: meloxicam, lactating goats, pharmacokinetics, intravenous and intramuscular injection, milk residue.

Introduction

Production of animal food derivatives safe for the human consumption is one of the most important issues of this century (Zylberman, 2004). On the other hand, society has become progressively more conscious about potential suffering in production animals and aware of the necessity of new pain therapies for its prevention and treatment (Giorgi *et al.,* 2016). Therefore, there is a demand for novel therapies to relieve pain in food producing animals (De Vito, 2015).

Nowadays, though domestic goats are present as a worldwide population in numbers large enough to confer a status of major species, these animals are still considered as a minor species by the regulatory agencies in Europe and the USA (Toutain *et al.,* 2010). Due to the lower number of goats compared to the other livestock species their health issues cannot be addressed with EMA or FDA-approved medications. Consequently, many drugs are administered to goats in an extra-label manner with no scientific information on drug behaviour, potential toxicity, and adequate withdrawal periods for drug removal from products marketed for human consumption (Clothier, 2010).

Meloxicam (MEL) is a potent anti-inflammatory drug having analgesic and antipyretic properties. MEL, has been shown to be preferential in inhibiting COX-2 (12 times more selective as a COX-2 inhibitor in the dog) than COX-1 isoenzyme (Kay *et al.,* 2000).

The pharmacokinetic profile of MEL shows good absorption, longer elimination half-life and high extravascular bioavailability in different animal species: dogs (Hare *et al.,* 2013; Montoya *et al.,* 2004; Busch *et al.,* 1998), cats (Lehr *et al.,* 2010; Giraudel *et al.,* 2005), horses (Lees *et al.,* 1991; Toutain and Cester, 2004; Toutain *et al.,* 2004; Burns *et al.,* 2010), rabbits (Turner *et al.,* 2006; Carpenter *et al.,* 2009), turtles (Di Salvo *et al.,* 2016), green iguanas (Divers *et al.,* 2010), piglets (Alassane *et al.,* 2010; Fosse and Spadavecchia, 2011), cattle (Johnn *et al.,* 2011; Coetzee *et al.,* 2009, 2012; Mosher *et al.,* 2012), camels (Wasfi *et al.,* 2012) and Ilamas (Amanda *et al.,* 2012). Little and conflicting information only is available for small ruminants (Shukla *et al*., 2007; Ingvast-Larssom *et al*., 2011; Wani *et al*., 2013; Wani *et al*., 2014).

The aim of the present study was two-fold: i) to determine the pharmacokinetics of MEL after intravenous (IV) and intramuscular (IM) route of administrations at the dose of 0.5 mg/kg b.w. in goats; ii) to quantify MEL residues in milk.

Materials and methods

Chemicals and reagents

The pure powder (purity >99.8%) of MEL was provided by LCG Promochem (Milan, Italy). The pure powder of piroxicam, the internal standard (IS), (> 99.8%) was provided by LCG Promochem (Milan, Italy). Acetonitrile (ACN), sodium chloride (NaCl), potassium dihydrogen phosphate (KH_2PO_4) and phosphoric acid (H_3PO_4) were used in the assays (Scharlau, Milan, Italy). All the other reagents and materials were provided from commercial sources.

Animals and experimental design

The animal experiment was approved by the animal welfare ethics committee of the University of Lublin (authorization 43/2017) and carried out in accordance with the European law (2010/63/UE).

Six healthy 1-2 year old mixed breed lactating goats, with an average weight of 55 (±4) kg were used in the study. Goats were examined to be clinically healthy based on blood analysis (CBC and serum biochemistry profile) and absence of any apparent clinical signs before the commencement of the study. All the animals were housed in an animal shed and were acclimatized to the new environment for 7 days. The animals were fed twice a day and water was provide *ad libitum.* The feed was withheld the night preceding the day of the experiment until 6 hr post drug administration.

Goats were randomly assigned to 2 treatment groups (6 slips of paper marked with the numbers from 1 to 6 in a box), using an open, single-dose, two-treatment, two-phase, unpaired, cross-over design (2x2 Latin square). On the day of experiment, the goats' necks were shaved and a local anaesthetic (Emla®, ointment, lidocaine 25 mg⁄g, prilocaine 25 mg⁄g; AstraZeneca) was spread on the skin above

the jugular veins. Two catheters were placed in the jugular veins, one in the left jugular for blood sampling in both the groups and a second one, only for the IV group, in the right jugular for drug administration. Group A (n=3) received a single dose of MEL (Metacam® solution for injection 20 mg/mL, Boehringer Ingelheim) at 0.5 mg/kg b.w. intravenously. Group B (n=3) received the same dose of MEL by an intramuscular injection in to the right gluteal muscle. A wash-out period of 3 weeks was observed between phases, the groups were rotated and the experiment was repeated. Blood samples (10 mL) were collected immediately before and at 5, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 10, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hr after administration of the drug in heparinised tubes. Goats were totally milked from both udders immediately before and after the administration of the drug at 10, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hr. After centrifugation at 4500xg for 10 min blood, plasma was harvested and samples (plasma and milk) were stored at -20 °C until use within 30 days from collection. A licensed veterinarian (BLW) evaluated the presence of likely adverse effects from the time of drug administration up to 7 days. Physical exam, changes in behaviour, food intake, heart rate and temperature were monitored and the injection site regularly examined for signs of inflammation.

High-Performance Liquid Chromatography

The HPLC method was based on a previously published technique (Kimble *et al.*, 2013) with slight modifications. The chromatographic separation assay was performed with a Gemini C18 analytical column (250 x 4.6 mm inner diameter, 5-µm particle size, Phenomenex) maintained at 25° C. The mobile phase consisted of ACN (A): 0.05 M phosphate buffer pH 3.2 (B) at an isocratic flow rate of 1 mL/min. The wavelength was set at 365 nm. The analytical method was re-validated for lactating goats' plasma and milk samples according to the EMA guidelines (2012) by examining the within-run precision calculated from similar responses for six repeats of 3 control samples (0.05, 0.5, and 1 µg/mL) in one run. The between-run precision was determined by comparing the calculated response of the low (0.05 µg/mL), middle (0.50 µg/mL), and high (1 µg/mL) control samples over three

consecutive daily runs (total of 6 runs). The assay accuracy for within-run and between-runs was established by determining the ratio of calculated response to expected response for low (0.05 μg/mL), middle (0.5 μg/mL), and high (1 μg/mL) control samples over 6 runs. Limit of quantitation (LOQ) was determined as signal-to-noise ratios of 10, and the limit of detection (LOD) as the signal-to-noise ratios of 3.

Quantification

MEL and IS singular stock solutions in ACN were prepared at the concentration of 1000 μg/mL, were diluted to reach a final concentration of 100 μg/mL and stored at -20 °C. MEL solution was diluted in glass tubes (10 mL) to reach final concentrations of 5, 2.5 and 1 μg/mL and were stored at 4° C. These last concentrations were then diluted to prepare a 7-point calibration curve at the following concentrations 2.5, 1, 0.5, 0.1, 0.05, 0.025 and 0.015 μg/mL of MEL in plasma and milk matrices. Standard curves were constructed with standard MEL concentrations *vs* ratio of MEL/internal standard peak areas. The analyte was stable for at least 20 weeks if stored at 4° C. Linearity of the regression curve for plasma and milk were assessed on the basis of the residual plot, the fit test and the back calculation. The efficiency of extraction method was evaluated by comparing the response (in area) of high, middle, low standards and the IS, spiked into blank plasma or milk, to the response of equivalent standards.

Preparation of plasma and milk samples

In a 15 mL polypropylene snap cap tube containing 500 μL of plasma, a volume of 100 μL of IS solution (10 μg/mL) was added. After vortexing, 2.2 mL of ACN was added to the samples and vortexed again. Finally, 0.1 gr of NaCl was added for the optimal separation of the organic and aqueous phases. After vortexing, samples were shaken for 10 min at 60 osc/min and then centrifuged for 10 min at 4500 g and the organic layer (2 mL) was transferred into a clean 5 mL polypropylene snap cap conical tube. The organic phase was evaporated under a gentle stream of nitrogen at 40 °C

and reconstituted with 200 µL of the mobile phase. Fifty µL of this latter solution was injected onto the HPLC system equipped with diode array detector.

Milk samples (500 µL each sample) were added to 100 µL of IS solution (10 µg/mL). After vortexing, 2.2 mL of ACN was added to the samples and vortexed again. Finally 0.1 gr of NaCl was added to optimize the separation of the organic and aqueous phases. After vortexing, samples were shaken for 10 min at 60 osc/min and then centrifuged for 10 min at 4500 g and the organic layer (2 mL) was transferred into a clean 5 mL polypropylene snap cap conical tube. The organic phase was evaporated under a gentle stream of nitrogen at 40 °C and reconstituted with 200 µL of the mobile phase. Fifty µL of this latter solution was injected onto the HPLC system equipped with diode array detector.

Pharmacokinetic analysis

MEL plasma concentration *vs* time curves were modelled for each subject using compartmental analysis (Gibaldi and Perrier, 1982). Comparison between competing models was made using the goodness of fit, Akaike's information criterion, Schwarz Bayesian information criterion, the sum of square of the residuals and the visual inspection of the curves. The pharmacokinetic calculations were carried out using WinNonlin v 5.3.1 (Pharsight, La Lolla, CA, USA). The elimination half-life (Beta_HL) was evaluated by ln2/beta while the elimination rate constant (K10) was estimated by the formula alpha*beta/K21. The half-life in milk was calculated according to a non-compartment model. Area under the plasma *vs* time curve (AUC) was calculated from 0 to the last quantifiable concentration using a linear trapezoidal method. For intravenous administration, plasma clearance (Cl) and the total volume of distribution at steady-state (Vss) were determined.

The IM bioavailability (F%) was calculated as:

$$F = \frac{AUC\ (IM)}{AUC\ (IV)}\ x\ 100$$

Afterwards, basing on the pharmacokinetic data, a WinNonlin 5.3.1 simulation was performed. It was executed to establish if multiple administrations of MEL to goats IM at 0.5 mg/kg once a day would

achieve the values of average therapeutic plasma concentration (MEC) reported in literature for cats (347 ng/mL), dogs (833 ng/mL) and horses (735 ng/mL). These latter values were calculated from approved maintenance dose and reported clearance values (Toutain *et al.,* 2004; Toutain and Lassourd, 2002). In agreement with the MEC values of MEL reported above, other PK/PD studies performed in cats and horses showed EC_{50} values of about 900 ng/mL and 195 ng/mL in horse and cat, respectively (Toutain and Cester, 2004; Giraudel *et al.,* 2005).

Statistical Analysis

The Kolmogorov-Smirnov test was applied to verify data distribution. Statistical comparison of PK parameters was determined with Student's t-test and performed by Graph Pad In Stat (Graph Pad Software). The PK parameters and MEL residues in milk are presented as means ± SD. In all experiments, differences were considered significant if $p< 0.05$.

Results

The HPLC method was revalidated using plasma and milk from control goats. Briefly, MEL concentration was linear in the range of 15–2500 ng/mL for both plasma and milk with correlation coefficients > 0.998. LOD was 5 ng/mL and LOQ was 15 ng/mL for both plasma and milk. When samples exceeded the upper limit of the range, they were re-analysed after appropriate dilution. The recoveries obtained were 89.3 ± 5.8% and 85.7 ± 3.2% for plasma and milk samples, respectively. The intra-day relative standard deviation for plasma and milk was lower than 4.6% and 5.1% respectively, whereas inter-day relative standard deviation was lower than 6.2% and 6.9%, respectively.

No visible adverse effects (changes in behaviour, appetite, heart rate, temperature and signs of inflammation at the injection site) were observed during the experiment.

Pharmacokinetics of meloxicam

Following IV and IM administrations of MEL at the dose of 0.5 mg/kg b.w, the plasma concentration *vs* time curves are illustrated in Figure 1. MEL plasma concentrations after IV and IM administrations were detectable up to 96 hr. At 120 hr, the drug concentrations dropped below the LOQ of the method. Pharmacokinetic parameters of MEL after IV injection were best fitted with the two-compartmental model, while a one-compartmental model best fitted plasma concentration after IM injection. MEL elimination phase from plasma was similar in both the administration groups. These similarities between routes of administration were proved by the pharmacokinetic parameters shown in Table 1 and 2. No pharmacokinetic parameters were shown to be significantly different between routes of administration. The bioavailability (F%) after IM administration was 105.0 ± 8.23%.

The plasma concentration *vs* time curve of the simulated multiple dose (0.5 mg/kg/day) of MEL by IM injection in goats is illustrated in figure 2. At the steady state, the AUC value was 32593 hr*ng/mL and the mean plasma concentration within 24 hr was 1358 ng/mL.

Disposition of MEL in milk

MEL concentrations following IV and IM injection at the dose of 0.5 mg/kg b.w. were quantifiable in the milk samples up to 60 and 48 hr, respectively (Figure 3). The average milk concentration showed similar trends between groups. The half-lives after both the administrations were not statistically different (9.6 ± 0.9 h, IV vs 9.3 ± 0.7h, IM)

Discussion

The primary objective of this study was to determine the pharmacokinetics of MEL in lactating goats after IV and IM administrations.

After IV administration the bi-compartment model provided the best fit of the concentration-time data while after IM injection the best fit was provide by the mono-compartment model. This difference can be triggered by a common phenomenon and is due to the value of the absorption rate

constant being similar or lower than the rate constant for the distribution phase. In this study, the absorption phase did not appear in the curves and the drug's disposition performed better with an open mono-compartment model (Gibaldi and Perrier, 1982).

Some information about MEL pharmacokinetics in goats and other small ruminant species is present in the literature (Shukla *et al.*, 2007; Ingvast-Larsson *et al.*, 2011; Wani *et al.*, 2013; Wani *et al.*, 2014). In the present study, the mean AUC value (26499 ± 4233 ng*hr/mL) was similar to data reported by Shukla *et al.*, (2007) (19230 ± 2230 ng*hr/mL) and Ingvast-Larsson *et al.*, (2011) (29738 ± 8576 ng*hr/mL) where goats received the same dose administered in the present study (0.5 mg/kg). In contrast, this value is in disagreement with data reported by Wani *et al.*, (2013), if normalized for the dose (2635 ± µg*hr/mL at the dose of 1 mg/kg b.w.). The mean half-lives of elimination obtained in the present study (9.96 and 10.82 hr) were similar to the values reported by Ingvast-Larsson *et al.*, (2011) (10.9 hr) but higher than those reported by Shukla *et al.*, (2007) (7 hr) and Wani *et al.*, (2013) (8 h). Finally, the mean values of Cl (19.38 ± 3.86 mL/hr/kg) and Vss (262.37 ± 50.74 mL/kg) obtained in the present study were in agreement with data reported by Ingvast-Larsson *et al.*, (2011) (Cl 17.9 ± 4.3 mL/hr/kg and Vss 245 ± 62 mL/kg) and Wani *et al.*, (2013) (Cl 22 mL/hr/kg and Vss 276 mL/kg). In contrast, Shukla *et al.*, (2007) reported a similar Vss value (250 mL/kg) but different plasma Cl (30 mL/hr/kg). These differences could be due to differences in weight (Shukla *et al.*, 2007 about 20 kg, Ingvast-Larsson *et al.*, 2011 about 44 kg, present study about 55 kg), variations in breed used in the diverse studies, and to the different LOQ of the analytical techniques (Toutain and Bousquet-Mélou, 2004).

Concerning the IM route of administration of MEL in goats, few data are reported in the literature. A study of Ingvast-Larssom *et al.*, (2011) presented an estimated half life of elimination value of 14.4 ± 5.2 hr obtained in 3 hornless goat kids after IM administration of MEL. This value represents an estimation of half life of elimination only, due to the small number of animals used and the small number of blood samples collected in that study. A similar mean half life of elimination value (10.82 ± 2.75 hr) was shown in the present study.

A dosage regimen of 0.5 mg/kg b.w. once a day by IM administration was simulated. The steady state was achieved after the third administration. The plasma concentration values at the steady state simulated in the present study were always above the MEC for cats (347 ng/mL). In contrast, the plasma concentrations of MEL were above the MEC value reported in dog (833 ng/mL) for 16 out of the 24 hrs. It should be keep in mind though that the mean plasma concentration within 24 hr (1358 ng/mL) obtained after the simulation was well above the MEC reported for dogs (833 ng/mL) or the EC50 in horse (900 ng/mL). However, further information is needed to determine the true MEC of meloxicam in goats.

The F% in this study is > 100%. This value can be explained as experimental error occurring during the different phases of the study. However, several other studies in the literature report a similar phenomena (Lee *et al*., 2017; Giorgi *et al*., 2013).

In conclusion, the relatively long half life of elimination, the complete F% of the IM injection and the high value of the mean plasma concentration within 24 hr calculated after simulation, suggests that the drug might be administered once a day by the IM route.

Disposition of MEL in milk

Few drugs are approved and labelled for lactating goats because of the likely drug residues in the milk. After a single dose of MEL by IV and IM administrations, the drug residues showed similar concentrations and a similar trend of elimination. This is in line with the similar trend of elimination reported for the plasma and the complete IM F%. Milk samples were collected in the present study until 168 h but MEL concentrations could only be quantified until 48h and 60h for IM and IV groups, respectively.

No maximum residual limits established for lactating goats are allowed in milk entering in the human food chain. Concerning the approval for use of MEL in bovine, EMEA/MRL/635/99-FILAL (1999) identified MEL as the marker residue and the ratio to total residues of 0.75 for milk. Moreover, in

cattle, after a recommended single dose of 0.5 mg/kg b.w. administered by IV or subcutaneous injection, the corresponding mean concentrations of MEL for low and high milk yields were 347 and 325 ng/mL, respectively. These values decline until the MRLs value (15 µg/kg) established for cattle is achieved at day 5 after the administration. Assuming the LOQ 15 ng/mL in the present study as a possible MRLs (Lin *et al.,* 2016), after IV and IM injection milk concentrations fell below the LOQ at 72 and 60 hr, respectively. The rate of depletion in goat's milk seems faster than that reported in cattle. These results could be due to the more active metabolism of goats compared with sheep or cattle (Toutain *et al.,* 2010). This is linked to their respective feeding behaviour where goats are natural browsers that can stand on their hind legs or even climb trees. They preferably eat leaves, shrubs, flowers and fruits, thus choosing the most nutritious available food but also the portions of plants containing many toxic alkaloids that need to be metabolised by a hepatic first pass effect. In contrast cattle are a non-selective bulk feeder that graze non selective grass generally low in term of alkaloid content (Toutain *et al.,* 2010).

Further studies are needed however to determine the milk concentrations after multiple administrations of MEL at 0.5 mg/kg once a day in a larger number of animals to determine the accurate withdrawal time for milk intended for human consumption (EMEA/MRL/635/99-FILAL, 1999; EMEA/CVMP/473/98-FINAL, 2000).

Conclusion

In conclusion, IV and IM administration of MEL in lactating goats showed similar pharmacokinetic profiles. The dose of 0.5 mg/kg used in the simulation study provided plasma concentrations above the MEC determined for other animal species for most of the 24 hr. This latter value along with the high IM F% and the long half-life of elimination suggested that the drug could be administered once a day. The present study showed that MEL concentrations in milk are to some extent in agreement

with the depletion of MEL in cattle milk. Further studies are required to clarify the dose needed to produce effective analgesia (MEC) and to avoid the risk of milk contamination in goats.

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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Figure' captions

Figure 1. Mean plasma concentration *vs* time curve of MEL after IV (—○—) and IM (—●—) administrations at 0.5 mg/kg in lactating goats (n=6). Bars represent the SD.

Figure 2. Mean plasma concentrations of MEL *vs* time curves following a simulated IM multiple dose rate at 0.5 mg/kg/day. The solid line (—) represents the MEC (833 ng/mL) of MEL in the dog; the square dotted line (⋯) represents the MEC (735 ng/mL) of MEL in the horse; the dash line (---) represents the MEC (347 ng/mL) of MEL in the cat (Toutain *et al.*, 2004; Toutain and Lassourd, 2002).

Figure 3. Disposition of MEL in milk after IV (—○—) and IM (—●—) administration at the dose of 0.5 mg/kg b.w. in lactating goats (n=6). Bars represent the SD.

Figure 1

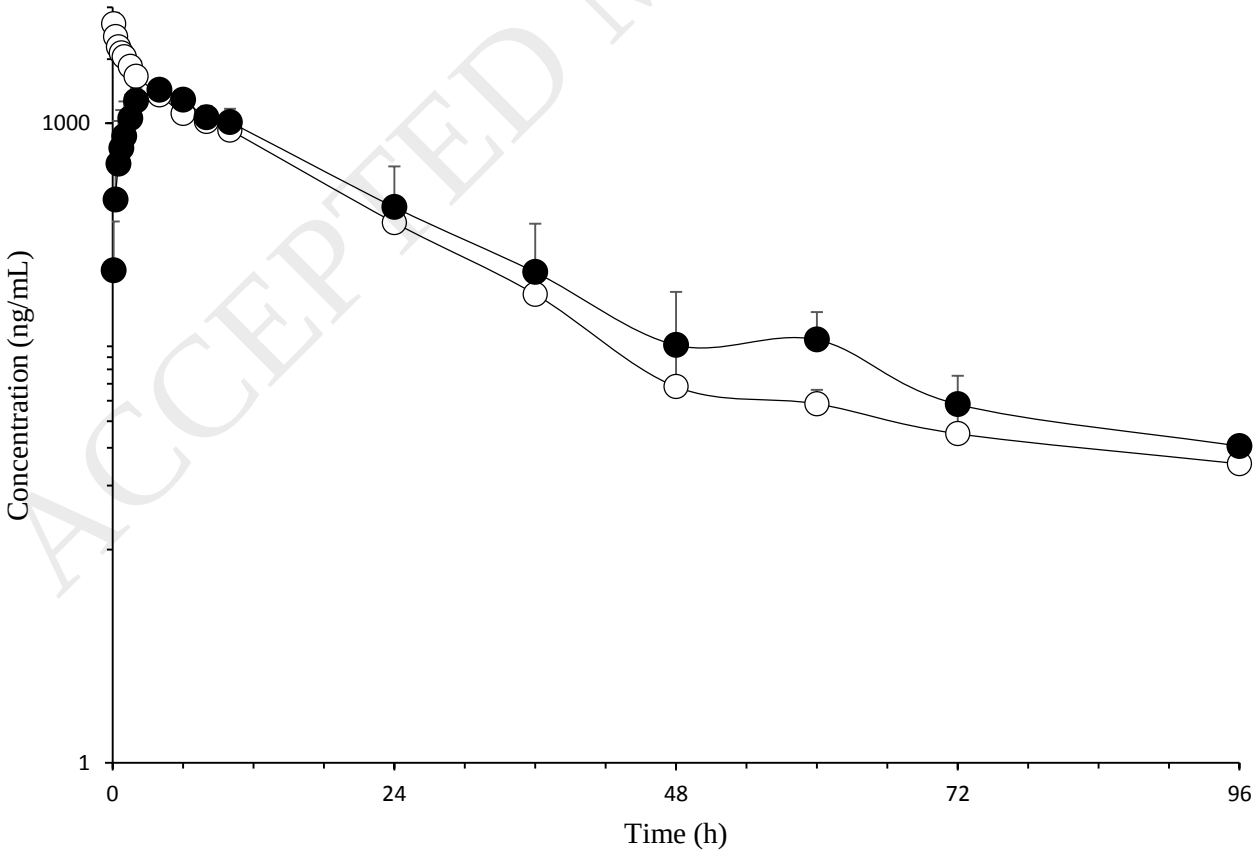


Figure 2

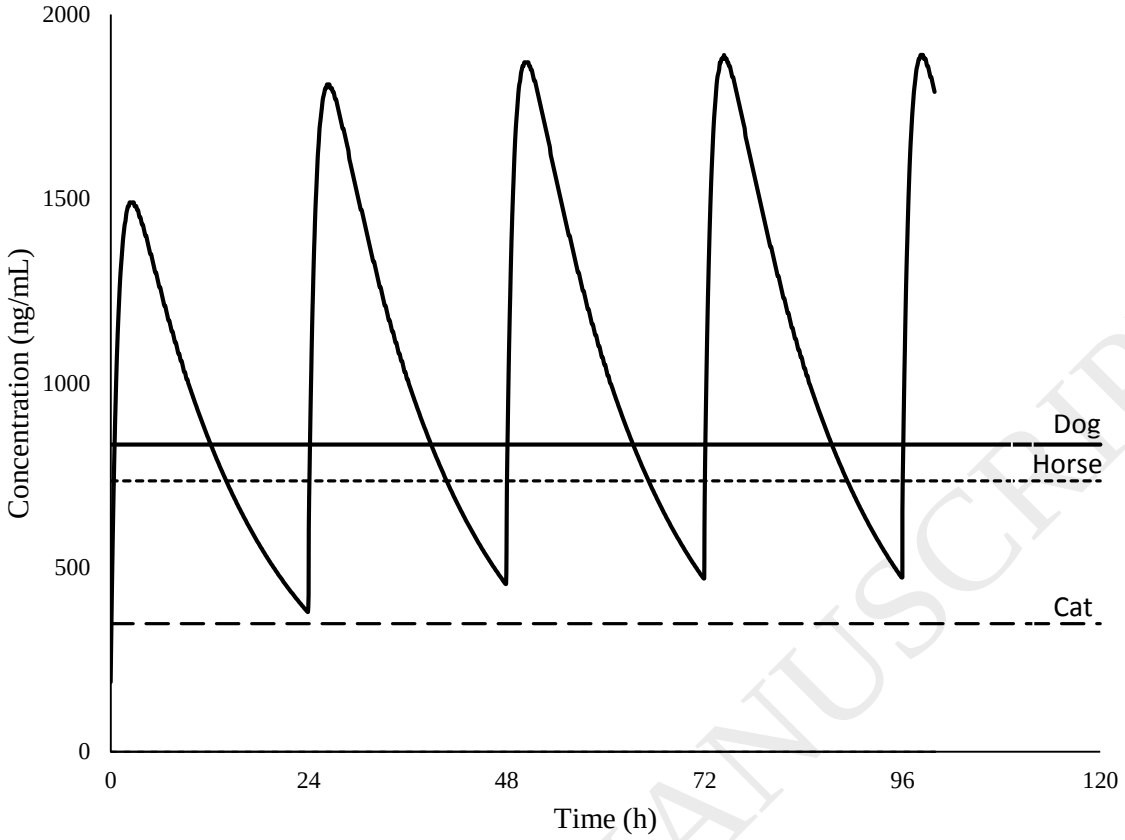
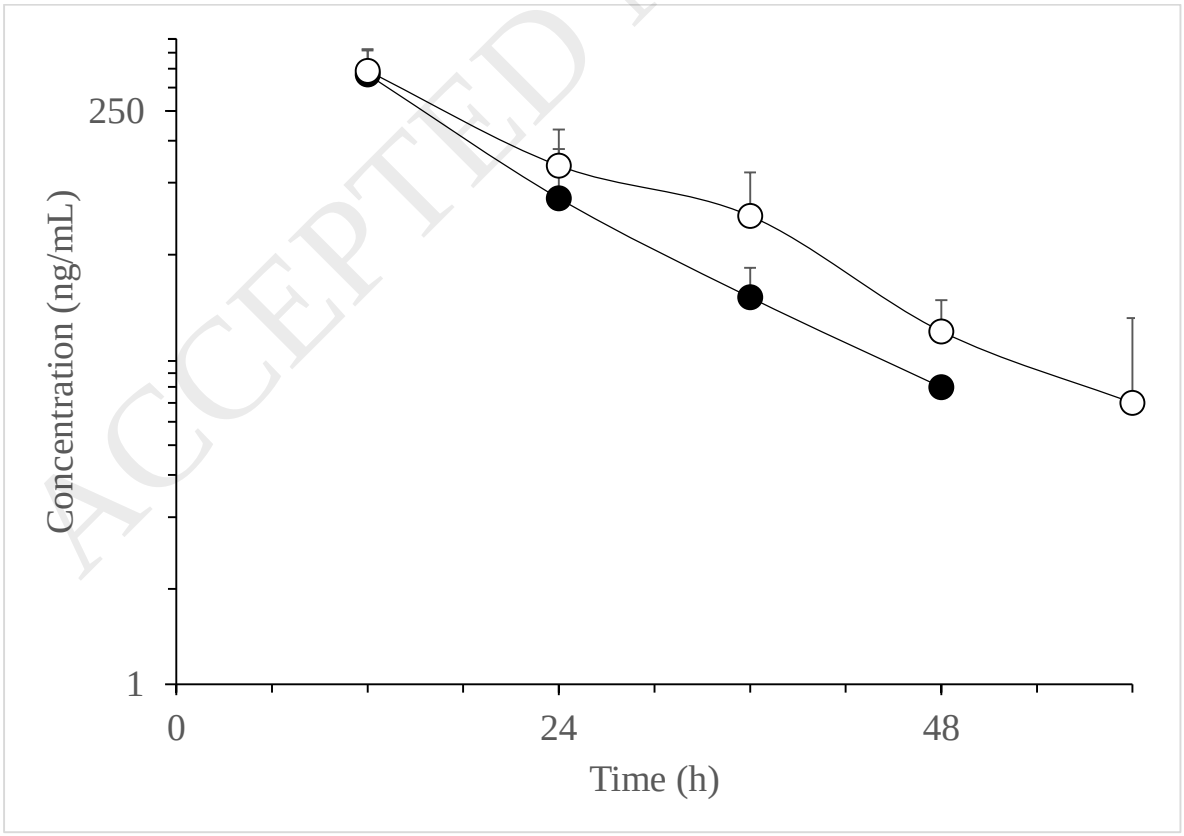


Figure 3



Table

Table 1

Pharmacokinetic parameters of MEL after IV administration at 0.5 mg/kg in lactating goats (n=6).

		IV		
Parameter	**Units**	**Mean**		**SD**
AUC	hr*ng/mL	26499	±	4233
K10	1/hr	0.12	±	0.03
K12	1/hr	0.64	±	0.38
K21	1/hr	1.13	±	0.71
K10_HL	hr	6.07	±	1.18
Alpha	1/hr	1.82	±	1.09
Beta	1/hr	0.07	±	0.02
Alpha_HL	hr	0.53	±	0.35
Beta_HL	hr	9.96	±	2.51
A	ng/mL	1223	±	153.71
B	ng/mL	1840	±	357.69
AUMC	hr*hr*ng/mL	374373	±	120223
MRT	hr	13.88	±	3.36
CL	mL/hr/kg	19.38	±	3.86
Vss	mL/kg	262.37	±	50.74
V1	mL/kg	165.76	±	23.06
V2	mL/kg	96.61	±	31.07

Area under the curve (AUC), elimination rate from compartment 1 (K10), rate of movement from compartment 1 to 2 (K12), the rate of movement from compartment 2 to 1 (K21), half-life of the elimination phase (K10_HL), rate constant associated with distribution (α), rate constant associated with elimination (β), distribution half-life (Alpha _HL), elimination half-life (Beta_HL), intercept for the distribution phase (A), intercept for the elimination phase (B), area under the first moment curve (AUMC), mean resident time (MRT); total clearance (CL), volume of distribution at the steady state (Vss), volume of compartment 1 (V1), and volume of compartment 2 (V2).

Table 2

Pharmacokinetic parameters of MEL after IM administration at 0.5 mg/kg in lactating goats (n=6).

		IM		
Parameter	**Units**	**Mean**		**SD**
Tmax	hr	3.73	±	2.08
Cmax	ng/mL	1409	±	40.78
AUC	hr*ng/mL	28071	±	7630
K01	1/hr	1.13	±	0.86
K10	1/hr	0.07	±	0.01
K01_HL	hr	1.08	±	0.76
K10_HL	hr	10.82	±	2.75
CL/F	mL/hr/kg	18.77	±	4.29
V/F	mL/kg	280.85	±	33.50
F%		105.93	±	8.23

Time to maximum plasma concentration (Tmax), maximum plasma concentration (Cmax), area under the curve (AUC), absorption rate (K01), elimination rate (K10), half-life of the absorption phase (K01_HL), half-life of the elimination phase (K10_HL), total body clearance per bioavailability (CL/F), apparent volume of distribution (V/F), and bioavailability (F%)