Received: 5 September 2019 | Revised: 19 October 2019 | Accepted: 27 October 2019

DOI: 10.1111/jvp.12826

ORIGINAL ARTICLE

JOURNAL OF Veterinary Pharmacology and Therapeutics WILEY

Pharmacokinetics and relative bioavailability of meloxicam oil suspension in pigs after intramuscular administration

Ying Li | Fanxi Guo | Xiangyuan Jiang | Juncai Ren | Yingxue Miao | Fangyi Ding | Zugong Yu

Laboratory of Veterinary Pharmacology and Toxicology, College of Veterinary Medicine, Nanjing Agricultural University, Nanjing, China

Correspondence
Zugong Yu, Laboratory of Veterinary Pharmacology and Toxicology, College of Veterinary Medicine, Nanjing Agricultural University, Nanjing 210095, China.
Email: yuzugong@njau.edu.cn

Funding information
Priority Academic Program Development of Jiangsu Higher Education Institutions

Abstract

This study aimed to develop one novel meloxicam (MEL) oil suspension for sustained-release and compare the pharmacokinetic characteristics of it with MEL conventional formulation in pigs after a single intramuscular administration. Six healthy pigs were used for the study by a crossover design in two periods with a withdrawal interval of 14 days. Plasma concentrations of MEL were measured by ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS). Pharmacokinetic parameters were calculated by noncompartmental methods. The difference was statistically significant ($p < .05$) between MEL oil suspension and MEL conventional formulation in pharmacokinetic parameters of mean residence time (6.16 ± 4.04) hr versus (2.66 ± 0.55) hr, peak plasma concentration (C_{max}) (0.82 ± 0.12) μg/ml versus (1.12 ± 0.22) μg/ml, time needed to reach C_{max} (T_{max}) (2.33 ± 0.82) hr versus (0.59 ± 0.18) hr, and terminal elimination half-life ($t_{1/2\lambda z}$) (3.74 ± 2.66) hr versus (1.55 ± 0.37) hr. The mean area under the concentration–time curve ($AUC_{0-\infty}$) of MEL oil suspension and MEL conventional formulation was 5.35 and 3.43 hr μg/ml, respectively, with a relative bioavailability of 155.98%. Results of the present study demonstrated that the MEL oil suspension could prolong the effective time of drugs in blood, thereby reducing the frequency of administration on a course of treatment. Therefore, the novel MEL oil suspension seems to be of great value in veterinary clinical application.

KEYWORDS

meloxicam oil suspension, pharmacokinetics, pigs, relative bioavailability, sustained-release

1 | INTRODUCTION

There is an increasing focus on analgesic treatment of production animals that are subjected to painful routine husbandry procedures (Fraser, 2008; Grandin, 2014; Hansen & Østerås, 2019; Moberg, 2000; Von Borell et al., 2009). For pigs, castration, tooth clipping, and tail amputation are common invasive husbandry procedures, to treat this pain in surgery, not only local anesthetics but also non-steroidal anti-inflammatory drugs (NSAIDs) are needed (Hay, Rue, Rue, Sansac, Brunel, & Prunier, 2004; Prunier, Mounier, Mounier, & Hay, 2005; Torrey, Devillers, Devillers, Lessard, Farmer, & Widowski, 2009). Moreover, conditions such as arthritis, traumatic injuries, pain after parturition, infected with influenza, and some metabolic diseases all show the demand for NSAIDs (Hoppes et al., 2013; Mainau & Manteca, 2011).

Meloxicam (MEL) [4-hydroxy-2-methyl-N-(5-methyl-2-thiomethyl)-2H-1,2-benzothiazide-3-formamide-1,1-dioxide], a new NSAID of enolamide class, which has remarkable analgesic and anti-inflammatory effects (Adawaren, Mukandiwa, Mukandiwa, Chipangura, Wolter, & Naidoo, 2019; Haiting Wang

& Tan, 2011; Naidu et al., 2004). It is a preferably cyclooxygenase-2 (COX-2) inhibitor with a lower incidence of gastrointestinal side effects and a faster onset effect compared with COX-nonselective NSAIDs or COX-1-selective NSAIDs (El-Awdan, Al-Shafeey, Al-Shafeey, Salam, El-Iraqy, & Kenawy, 2015; Khan, Paulson, Paulson, Verburg, Lefkowith, & Maziasz, 2002; Lihua Cao, 2011; Louder et al., 2011; da Silveira, Fiorot, Fiorot, Xavier, Yoshida, & Oliveira, 2018; Urayama et al., 2019). Approved formulations include MEL oral suspension, injectable solution, and transmucosal oral spray. In EMEA, MEL has been licensed for use of cattle, cats, dogs, pigs, and horses. Though MEL conventional formulation has a good effect in veterinary clinical application, its high peak concentration may cause damage to animals (Cetinkal et al., 2010; Uzun, Atli, Atli, Perk, Burukoglu, & Ilgin, 2015). And the short elimination half-life of it may require a second administration in a 3–5 days course of common disease or chronic diseases. Repeated administration could result in animal stress, increasing labor costs and material resources, which shows the urgently needed of long-acting MEL preparations.

Oil suspension is simple to prepare, having lower irritation and higher safety than other injections, promoting it into a traditional form of sustained-release formulation (Larsen, Thing, & Larsen, 2012; Duong, Maeng, Duong, Maeng, & Chi, 2019). In the meantime, it has the advantage of sustained-release so that prolongs the action time of the drug and reduces the frequency of drug delivery, determining the feasibility of the dosage form in the veterinary clinic. Amoxicillin and ceftiofur hydrochloride oil suspension are typical representations of it (He et al., 2011; Hibbard et al., 2002; Tang et al., 2010; Xiong et al., 2018).

Based on the above considerations, we tried to prepare MEL oil suspension. The purpose of this study was to evaluate the pharmacokinetic characteristics of MEL oil suspension and compare it with MEL conventional formulation in pigs after a single-dose intramuscular administration to obtain the relative bioavailability, on the basis, to explore the prospect of its veterinary clinical application.

2 | MATERIALS AND METHODS

2.1 | Drugs and reagents

Meloxicam analytical standard (99.9%) (Batch No. 100679-201102) was purchased from National Institutes for Food and Drug Control. 2% (w/v) MEL injection (Batch No: J21015 A-14) was purchased from Boehringer Ingelheim. MEL bulk drug with a chemical purity of 99% (No. 151005) was produced and provided by Shandong Xinhua Pharmaceutical Co., Ltd. Of 2% (w/v) MEL oil suspension was homemade. Acetonitrile and formic acid were of high-performance liquid chromatography (HPLC) grade, which was purchased from Merck Corporation and Anaqua Chemical Supply, respectively. All other reagents used for extraction and analysis were analytical reagent grade or better.

2.2 | Preparation of MEL oil suspension

Of 2% MEL oil suspension was comprised of the injection of soybean oil as a dispersion medium and an appropriate amount of span 60 and wax as excipients. It was prepared by the conventional suspension preparation method (Xide & Zhu, 2002) and sterilized for 30 min at 100° at the end. The appearance of MEL oil suspension was yellow, which would precipitate after long-laid and could be redistributed evenly after shaking.

2.3 | Animals

Six pigs (three males and three females) were procured from Nanjing Liuhe District Experimental Pig Farm. All of the animals did not receive any drugs during the experiments. These pigs were deemed to be normal and clinically healthy after having a regular clinical examination. All the animals were raised with water and drug-free feed to acclimatize for a week prior to the drug administration. On the day of the MEL injection, the mean body weight (b.w.) of pigs was 13–15 kg. All the experimental procedures involving animals were conducted following the guidelines of Nanjing Agricultural University (Nanjing, China) Animal Ethics Committee.

2.4 | Experimental design

Six pigs went through an acclimatization period of 7 days before the pharmacokinetic experiment. Before MEL was administrated, all pigs were weighed and blood samples were drawn from the jugular vein. The study was carried out in a crossover design in two periods with a withdrawal interval of 14 days. In the first period, six pigs were randomized into two groups with three pigs each, one group receiving a single 0.4 mg/kg b.w. MEL oil suspension and the other group receiving a single 0.4 mg/kg b.w. MEL conventional formulation. In the second period, six pigs were administrated the opposite drug with the first period. Plasma samples (4 ml) were collected into tubes containing heparin at 0.42, 1, 2, 3, 3.5, 4, 4.5, 6, 8, 12, 24, 30, 36, 48, 54, 60, 72, and 78 hr after intramuscular administering MEL oil suspension, and plasma samples (4 ml) were collected at 0.17, 0.42, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24, 30, 36, 48, 54, 60, 72, and 78 hr after intramuscular administering MEL conventional formulation. All samples were centrifuged at 4,000 *g* for 10 min within 2 hr after collection. Each plasma sample was stored frozen at −20°C until measured by UPLC-MS/MS.

2.5 | Analytical method

2.5.1 | UPLC conditions

The Waters Acquity™ UPLC system (Waters) was used in this study. The column used was an Acquity UPLC BEH C_{18} column (50 mm × 2.1 mm,

1.7 μm), and the column temperature was maintained at 35°C. The mobile phase was a mixture of 0.1% formic acid–water (mobile phase A) and acetonitrile (mobile phase D) with a gradient elution at a flow rate of 0.25 ml/min (Table 1). The analytical run time was 5.50 min. Data acquisition and integration were performed by Masslynx4.1 (Waters).

2.5.2 | MS/MS parameters

The analysis was carried out by electrospray ionization operated in positive polarities, and data were gathered by multiple reaction monitoring (MRM) mode. Two transitions compounds were monitored. Table 2 showed the MS/MS parameters of the investigated analytes.

2.5.3 | Sample preparation

The frozen plasma samples were thawed at room temperature. One millilitre of acetonitrile was added to 200 μl blood plasma in the tubes, then vortexed for 3 min and centrifuged at 8,000 *g* for 8 min. The upper layer was transferred into a clean tube, repeated the extraction procedure of the underlying layer, and combined the supernatant. The organic layer was dried under nitrogen in a thermostat water bath at 40°C. The initial mobile phase (1 ml) was used to dissolve the residue. Ultimately, the samples were vortex-mixed for 3 min and filtered through membrane filters with a pore size (0.22 μm). Five micorlitres of the final samples was injected into a UPLC-MS/MS system to analyze.

2.6 | Method validation

2.6.1 | Specificity

Blank plasma samples, blank plasma samples supplemented with three different concentrations of MEL (low, medium, and high concentration), and plasma from pigs that had been administered with MEL were analyzed to observe whether there existed interference in the elution positions of MEL.

Linearity and linearity range. A stock solution (200 μg/ml) of MEL was prepared in acetonitrile and diluted with the initial mobile phase solution to series of standard solutions of 20, 50, 100, 500, 1,000, 2,000, and 5,000 ng/ml. Blank plasma samples were mixed with the corresponding MEL standard solutions to prepare plasma standard samples and to analyze. The standard curve of MEL from 2 to 500 ng/ml was detected by UPLC-MS/MS system. The linear regression, coefficient variation, and recovery were also calculated.

TABLE 1 Gradient UPLC method

Time (min)	% Mobile phase A	% Mobile phase D	Flow rate (ml/min)
0.00	30.0	70.0	0.25
1.00	30.0	70.0	0.25
1.10	90.0	10.0	0.25
4.00	90.0	10.0	0.25
4.10	30.0	70.0	0.25
5.50	30.0	70.0	0.25

2.6.2 | Limits of detection and limits of quantification

The limits of detection (LODs) and limits of quantification (LOQs) were required to produce a peak with a signal/noise ratio of threefold and tenfold, respectively. The LOQ was the lowest concentration on the standard curve that can be measured with acceptable accuracy (relative standard deviation, RSD < 20%).

2.6.3 | Extraction recovery

Blank plasma samples supplemented with low, medium, and high concentrations of MEL (5, 50, and 500 ng/ml) were prepared. Each of the concentrations was measured five times. The recovery was evaluated by comparing the peak areas as the signal intensities of the mass fragment in the spiked samples.

2.6.4 | Precision

The samples prepared as mentioned in the extraction recovery test were analyzed for three consecutive days. The intraday and interday precision were defined by the relative standard deviation (RSD).

2.7 | Pharmacokinetic analysis

Descriptive pharmacokinetic parameters were determined with WinNonlin Professional software (Version 5.2; Pharsight) by noncompartmental analysis. Lambda z was a first-order rate constant associated with the terminal (log-linear) segment of the curve. It was estimated by the linear regression of the terminal data points. The terminal elimination half-life ($t_{1/2\lambda z}$) was calculated by $t_{1/2\lambda z} = 0.693/\lambda z$. Areas under the plasma concentration–time curves ($AUC_{0-\infty}$) were calculated by the method of trapezoids. The maximum plasma concentrations (C_{max}) of the drug and times to C_{max} (T_{max}) were obtained from the plasma concentration versus time data.

2.8 | Statistical analysis

All results were presented as mean ± *SD*. The pharmacokinetic parameters determined were compared by one-way analysis of

TABLE 2 MS/MS parameters for determination of the investigated analytes

Compound	Transition	Polarity	Collision voltage (eV)	Retention time (min)
MEL	351.9443 > 140.9115	Positive	18	5.50
	351.9443 > 114.9086	Positive	20	5.50

variance using statistical software (SPSS version 12; SPSS Inc.). In all cases, $p < .05$ was considered statistically significant. The relative bioavailability (F) of MEL was calculated by the following equation:

$$F = \frac{AUC_T \times D_R}{AUC_R \times D_T} \times 100\%$$

AUC_T is the mean area under the concentration–time curve of MEL oil suspension; AUC_R is the mean area under the concentration–time curve of MEL conventional formulation; D_T is the dose of MEL oil suspension; and D_R is the dose of MEL conventional formulation.

3 | RESULTS

3.1 | Animals

No abnormalities or adverse effects were noted in any pigs during the whole pharmacokinetic trial after MEL oil suspension and MEL conventional formulation administration.

3.2 | Analytical method

The UPLC-MS/MS method that we developed to detect MEL in plasma had high selectivity, sensitivity, accuracy, precision, and simplicity. No interference was observed at the elution positions of MEL (Figure 1). A linear relationship existed in the calibration curve over the range of 2–500 ng/ml with a correlation coefficient of 0.9995 (Figure 2). The LODs and LOQs were 0.5 and 2 ng/ml, respectively. As was shown in Tables 3 and 4, the extraction recovery of MEL was 85.06%–106.94% and the RSD was 0.79%–7.36%. The interday precisions (RSD) for three concentrations (5, 50, and 500 ng/ml) were 7.36%, 2.11%, and 1.57%, respectively.

3.3 | Pharmacokinetics

Mean plasma MEL concentration versus time curves for oil suspension and conventional formulation after intramuscular administration are presented in Figure 3. The mean pharmacokinetic parameters of MEL oil suspension and MEL conventional formulation were obtained from an analysis of the curves that have been shown in Table 5. There were significant differences ($p < .01$) between MEL oil suspension and MEL conventional formulation in pharmacokinetic parameters of $t_{1/2\lambda z}$ and mean residence time (MRT). Meanwhile, there was a highly significant difference ($p < .001$) between MEL oil suspension and MEL conventional formulation in T_{max}, which was 2.33 ± 0.82 hr and 0.59 ± 0.18 hr, respectively. The $AUC_{0-\infty}$ of MEL oil suspension was 5.35 ± 2.57 μg hr/ml, while the $AUC_{0-\infty}$ of MEL conventional formulation was 3.43 ± 1.00 μg hr/ml. MRT of MEL oil suspension was 6.16 ± 4.04 hr, which significantly longer than MEL conventional formulation. The mean C_{max} following intramuscular administration of MEL oil suspension and MEL conventional formulation differed statistically with a value of 0.82 and 1.12 μg/ml at 2.33 and 0.59 hr, respectively.

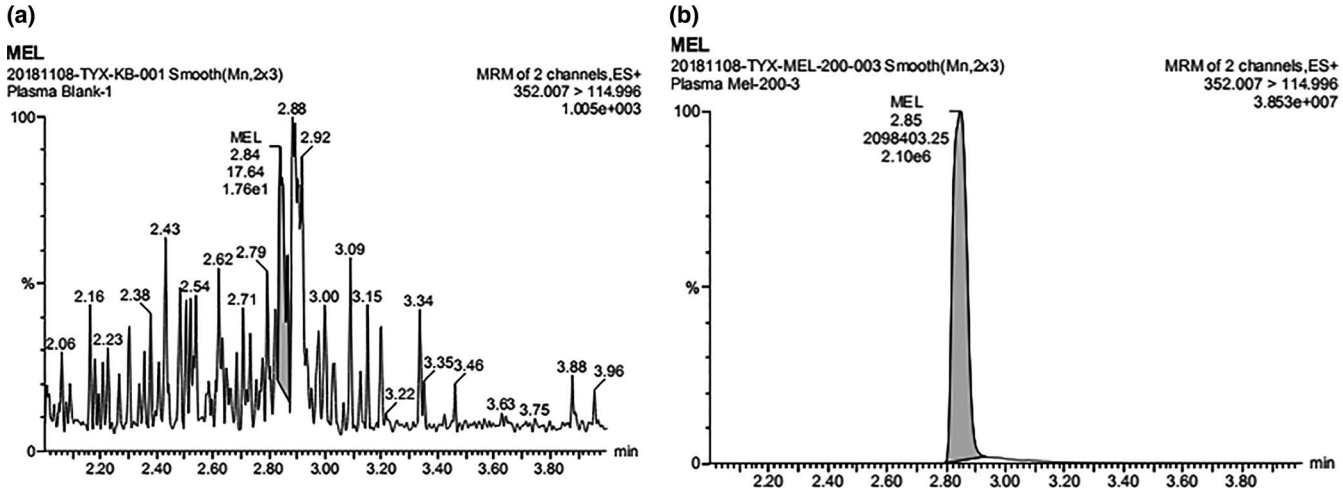

FIGURE 1 MRM chromatograms for MEL in plasma by UPLC-MS/MS of blank plasma sample (a) and blank plasma spiked with MEL (b)

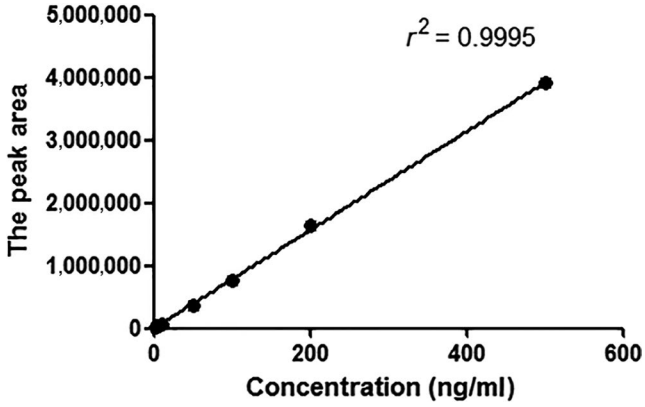

FIGURE 2 Linear standard curve over the range of 2–500 ng/ml with a correlation coefficient of 0.9995

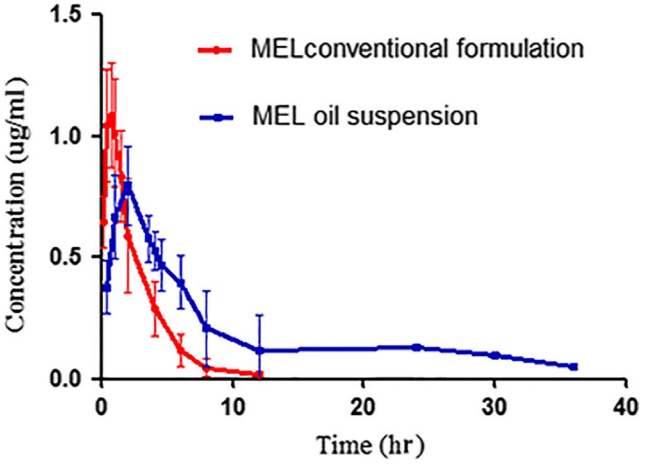

FIGURE 3 Plasma concentration–time profile of MEL oil suspension and conventional formulation in pigs after a single intramuscular dose of 0.4 mg/kg b.w. (mean ± *SD*, *n* = 6)

TABLE 3 The recovery data for assay of MEL in plasma (intraday, *n* = 5)

	Recovery (%)		
Concentration (ng/ml)	Intraday 1 (*n* = 5)	Intraday 2 (*n* = 5)	Intraday 3 (*n* = 5)
5	100.27	85.06	103.79
	99.29	87.64	100.73
	98.77	89.39	105.45
	98.77	87.65	99.01
	100.90	88.98	106.94
50	103.51	103.05	101.99
	102.35	98.91	101.19
	101.45	98.49	105.11
	103.34	99.54	102.09
	101.31	98.27	104.79
500	92.11	92.66	94.92
	94.18	92.61	92.79
	95.03	93.90	97.53
	92.21	92.42	92.50
	93.03	93.89	94.48

4 | DISCUSSION

We developed a new determination method in this experiment by UPLC-MS/MS on account of the low MEL plasma concentrations. This method was validated for specificity, linearity, LODs, LOQs, extraction recovery, and precision; all results were up to the standard of bioanalytical method validation (FDA, 2019). The LOQs of this method could reach 2 ng/ml, which was more sensitive than 10.2 ng/ml (Tian et al., 2018) and 20 ng/ml (Rigato, 2006) that reported in the literature, indicating high sensitivity. It has been successfully applied to the pharmacokinetic study of MEL in pigs.

Based on the market demand and the advantages of oil suspension, we prepared MEL oil suspensions. In this study, we compared the pharmacokinetic parameters of MEL oil suspension with commercially available MEL formulation by intramuscular administration and determined the relative bioavailability. The crossover design excluded interindividual variations between the two MEL formulations. The washout period was sufficient because blood samples withdrawn before the next administration confirmed that MEL was no longer detected. The dose administered in this trial was 0.4 mg/kg, which was based on the recommended dosage of MEL conventional formulation.

Pharmacokinetic parameters of MEL oil suspension and MEL conventional formulation were compared; the mean $t_{1/2\lambda z}$ of MEL oil suspension following intramuscular administration was 3.74 hr, which was prolonged compared with 1.55 hr of MEL conventional formulation, showing that MEL oil suspension had a certain sustained-release effect. The study of Fosse et al. (2010) (0.6 mg/kg) obtained the mean $t_{1/2\lambda z}$ of MEL conventional formulation that was 2.6 hr, which was also lower than the value of 3.75 hr. Meanwhile,

TABLE 4 Precision and accuracy data for assay of MEL in plasma (intraday, *n* = 5; interday, *n* = 5 series per day, 3 days)

		Precision, RSD (%)			
Concentration (ng/ml)	Recovery (%)	Intraday 1 (*n* = 5)	Intraday 2 (*n* = 5)	Intraday 3 (*n* = 5)	Interday (*n* = 15)
5	96.84 ± 7.13	0.99	1.93	3.18	7.36
50	101.69 ± 2.15	1.00	1.97	1.73	2.11
500	93.62 ± 1.47	1.36	0.79	2.14	1.57

TABLE 5 Pharmacokinetic parameters (mean ± *SD*, *n* = 6) of MEL oil suspension and MEL conventional formulation in pigs after an intramuscular dose of 0.4 mg/kg b.w

Parameter	Value for the indicated group	
	MEL conventional formulation	MEL oil suspension
λz (1/hr)	0.47 ± 0.11	0.24 ± 0.10*
$t_{1/2\lambda z}$ (hr)	1.55 ± 0.37	3.74 ± 2.66**
C_{max} (μg/ml)	1.12 ± 0.22	0.82 ± 0.12*
T_{max} (hr)	0.59 ± 0.18	2.33 ± 0.82**
AUC_{0-t} (hr μg/ml)	3.37 ± 0.98	5.02 ± 2.39
$AUC_{0-\infty}$ (hr μg/ml)	3.43 ± 1.00	5.35 ± 2.57
MRT (hr)	2.66 ± 0.55	6.16 ± 4.04**
V_d (ml/kg)	269.44 ± 52.14	380.69 ± 82.10*
CL (ml/hr/kg)	125.76 ± 38.01	85.54 ± 27.99
F (%)	—	155.98

Note: λz, terminal phase rate constant; $t_{1/2\lambda z}$, terminal elimination half-life; C_{max}, peak plasma concentration; T_{max}, time needed to reach C_{max}; AUC_{0-t}, the mean area under the concentration–time curve from 0 hr to last time collected samples; $AUC_{0-\infty}$, the mean area under the concentration–time curve from 0 hr to infinity; MRT, mean residence time; V_d, volume of distribution at the steady state; CL, plasma clearance; F, relative bioavailability.

*Statistical difference between MEL oil suspension and MEL conventional formulation ($p < .05$);

**Statistical difference between MEL oil suspension and MEL conventional formulation ($p < .01$);

***Statistical difference between MEL oil suspension and MEL conventional formulation ($p < .001$).

the blood concentrations of MEL oil suspension were detected over 36 hr, while the blood concentrations of MEL conventional formulation were detected just 12 hr, revealing an obvious long-term tendency of MEL oil suspension. The mean Cl and MRT of MEL oil suspension were 85.54 ml hr^{-1} kg^{-1} and 6.16 hr, respectively, and the mean Cl and MRT that observed from MEL conventional formulation were 125.76 ml hr^{-1} kg^{-1} and 2.66 hr, respectively. The lower Cl and the higher MRT were consistent with the result of the long-term trend of MEL oil suspension. The mean T_{max} of MEL oil suspension was 2.33 hr, which was significantly delayed compared with 0.59 hr of MEL conventional formulation, indicating the sustained-release of MEL oil suspension. The $AUC_{0-\infty}$ of MEL oil suspension was higher than that of MEL conventional formulation at the same dosage with a mean bioavailability of 155.98%, which demonstrated that the MEL oil suspension we developed could be absorbed well after intramuscular injection.

There were few data reported in the literature regarding the intramuscular administration route of MEL in pigs, but studies have been carried out on the pharmacokinetics of MEL via intravenous administration extensively, and results showed that the $t_{1/2\lambda z}$ of MEL in plasma were 2.7 hr (0.4 mg/kg) in pigs (Fosse et al., 2010); 20.35 hr (0.5 mg/kg) and 21.86 hr (0.5 mg/kg) in calves (Coetzee, Kukanich, Kukanich, Mosher, & Allen, 2009; Coetzee et al., 2012); 5.29 hr (0.5 mg/kg) in horses (Pierre-Louis & Cester, 2004); 8.08 hr (1 mg/kg), 6.73 hr (0.5 mg/kg), and 9.96 hr (0.5 mg/kg) in goats (De Vito et al., 2018; Shukla et al., 2007; Wani, Roy, Roy, Ashraf, & Roy, 2013); 11.54 hr (0.1 mg/kg) in beagle dogs (Junyi Hao & Cao, 2017); 3. 69 hr (1.5 mg/kg) in guinea pigs (Moeremans, Devreese, Devreese, Baere, Croubels, & Hermans, 2019); and 6.41 hr (10 mg/kg) in mice (Busch et al., 1998), revealing great interspecific variability. Besides, according to the record of EMEA, after two intramuscular doses of 0.4 mg/kg MEL conventional formulation, a C_{max} value of 1.9 μg/ml was reached after 1 hr in pigs, the mean $t_{1/2\lambda z}$ was approximately 2.5 hr (EMEA, 2019). All the results showed that the $t_{1/2\lambda z}$ of MEL in pigs was shorter than other animals, exhibiting the rapid metabolism of MEL in pigs.

This study only evaluated the pharmacokinetics and relative bioavailability of MEL oil suspension, and its conventional formulation in pigs, however, did not conduct an in-depth study on its metabolic mechanism in pigs about the rapid metabolism. Meanwhile, though the pharmacokinetic profile of MEL oil suspension was relative desirable, the longer $t_{1/2\lambda z}$ and the lower C_{max} indicated that the residue experiment and the efficacy study are needed to determine the withdrawal time and the therapeutic concentration of MEL oil suspension in pigs.

5 | CONCLUSION

The study investigated the pharmacokinetics and relative bioavailability of MEL oil suspension and MEL conventional formulation in pigs at a single dose of 0.4 mg/kg. The results showed that the MEL oil suspension had a long-term trend than the conventional formulation, demonstrating that the self-developed MEL oil suspension was feasible. Further studies are warranted to clarify the efficacy and safety of MEL oil suspension.

ACKNOWLEDGMENTS

This study was supported by the Priority Academic Program Development of Jiangsu Higher Education Institution (PAPD).

CONFLICT OF INTEREST

The authors have no professional or financial conflicts of interest to declare.

AUTHOR CONTRIBUTION

YL and ZY proposed the pharmacokinetic study protocol. YL, FG, JR, XJ, FD, and YM participated in the experiments. YL, XJ, and JR

contributed to sample preparation and data analysis. ZY and FG edited and reviewed the final version of the article. All authors provided constructive comments on the manuscript.

ORCID

Zugong Yu https://orcid.org/0000-0003-1643-2206

REFERENCES

Adawaren, E. O., Mukandiwa, L., Chipangura, J., Wolter, K., & Naidoo, V. (2019). Percentage of faecal excretion of meloxicam in the Cape vultures (*Gyps corprotheres*). *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, *215*, 41–46.

Busch, U., Schmid, J., Heinzel, G., Schmaus, H., Baierl, J., Huber, C., & Roth, W. (1998). Pharmacokinetics of meloxicam in animals and the relevance to humans. *Drug Metabolism and Disposition*, *26*(6), 576–584.

Cetinkal, A., Colak, A., Topuz, K., Demircan, M. N., Simsek, H., Berber, U., … Vatansever, H. S. (2010). The effects of meloxicam on neural tube development in the early stage of chick embryos. *Turkish Neurosurgery*, *20*(2), 111–116.

Coetzee, J. F., Kukanich, B., Mosher, R., & Allen, P. (2009). Pharmacokinetics of intravenous and oral meloxicam in ruminant calves. *Veterinary Therapeutics Research in Applied Veterinary Medicine*, *10*(4), E1.

Coetzee, J. F., Mosher, R. A., KuKanich, B., Gehring, R., Robert, B., Reinbold, J. B., & White, B. J. (2012). Pharmacokinetics and effect of intravenous meloxicam in weaned Holstein calves following scoop dehorning without local anesthesia. *BMC Veterinary Research*, *8*(1), 153. https://doi.org/10.1186/1746-6148-8-153

da Silveira, L. M., Fiorot, A. B., Xavier, T. P., Yoshida, M. I., & de Oliveira, M. A. (2018). Drug-excipient compatibility assessment of solid formulations containing meloxicam. *European Journal of Pharmaceutical Sciences*, *112*, 146–151. https://doi.org/10.1016/j.ejps.2017.11.015

De Vito, V., Łebkowska-Wieruszewsk, B., Lavy, E., Lisowski, A., Owen, H., & Giorgi, M. (2018). Pharmacokinetics of meloxicam in lactating goats (*Capra hircus*) and its quantification in milk after a single intravenous and intramuscular injection. *Small Ruminant Research*, *160*, 38–43. https://doi.org/10.1016/j.smallrumres.2018.01.001

El-Awdan, S. A. W., Al-Shafeey, N., Salam, O. A., El-Iraqy, W. I., & Kenawy, S. A. B. (2015). Modulation of the pharmacological properties of meloxicam by octreotide in rats. *Journal of Saudi Chemical Society*, *19*(2), 123–132. https://doi.org/10.1016/j.jscs.2012.01.002

EMEA (2019). *European Agency for the Evaluation of Medicinal Products. Metacam*. Retrieved from https://www.ema.europa.eu/en/documents/product-information/recocam-epar-product-information_en.pdf

FDA (2019). *Bioanalytical method validation*. Retrieved from https://www.regulations.gov/document?D=FDA-2019-D-1469-0002

Fosse, T. K., Haga, H. A., Hormazabal, V., Haugejorden, G., Horsberg, T. E., & Ranheim, B. (2010). Pharmacokinetics and pharmacodynamics of meloxicam in piglets. *Journal of Veterinary Pharmacology & Therapeutics*, *31*(3), 246–252.

Fraser, D. (2008). Understanding animal welfare. *Acta Veterinaria Scandinavica*, *50*(1), S1. https://doi.org/10.1186/1751-0147-50-S1-S1

Grandin, T. (2014). Animal welfare and society concerns finding the missing link. *Meat Science*, *98*(3), 461–469. https://doi.org/10.1016/j.meatsci.2014.05.011

Haiting Wang, C. L., & Tan, B. (2011) Clinical application of meloxicam in pig farms. *Pig Raising*, *1*, 84–85.

Hansen, B. G., & Østerås, O. (2019). Farmer welfare and animal welfare-Exploring the relationship between farmer's occupational well-being and stress, farm expansion and animal welfare. *Preventive Veterinary Medicine*, *170*, 104741.

Hay, M., Rue, J., Sansac, C., Brunel, G., & Prunier, A. (2004). Long-term detrimental effects of tooth clipping or grinding in piglets: A histological approach. *Animal Welfare*, *13*(1), 27–32.

He, J., Tang, S., Li, L., Zhang, C., Li, X., Xia, X., & Xiao, X. (2011). Pharmacokinetics of a novel amoxicillin/colistin suspension after intramuscular administration in pigs. *Journal of Veterinary Pharmacology and Therapeutics*, *34*(1), 42–50. https://doi.org/10.1111/j.1365-2885.2010.01191.x

Hibbard, B., Robb, E. J., Chester, S. T. Jr, Dame, K. J., Boucher, J. F., & Alaniz, G. R. (2002). Dose determination and confirmation of a long-acting formulation of ceftiofur (ceftiofur crystalline free acid) administered subcutaneously for the treatment of bovine respiratory disease. *Journal of Veterinary Pharmacology and Therapeutics*, *25*(3), 175–180. https://doi.org/10.1046/j.1365-2885.2002.00403.x

Hoppes, S., Heatley, J. J., Guo, J., Turner, D., Shivaprasad, H. L., & Tizard, I. (2013). Meloxicam treatment in cockatiels (*Nymphicus hollandicus*) infected with avian bornavirus. *Journal of Exotic Pet Medicine*, *22*(3), 275–279. https://doi.org/10.1053/j.jepm.2013.08.014

Junyi Hao, N. Y., & Cao, X. (2017). Pharmacokinetics and Bioavailability of Meloxicam Tablets in Beagle Dogs. *Chinese Journal of Veterinary Medicine*, *51*(7), 47–51.

Khan, K. N. M., Paulson, S. K., Verburg, K. M., Lefkowith, J. B., & Maziasz, T. J. (2002). Pharmacology of cyclooxygenase-2 inhibition in the kidney. *Kidney International*, *61*(4), 1210–1219. https://doi.org/10.1046/j.1523-1755.2002.00263.x

Larsen, S. W., Thing, M. A., & Larsen, C. (2012).Oily (lipophilic) solutions and suspensions. In J. C. Wright, & D. J. Burgess (Eds.), *Long acting injections and implants* (pp. 113–135). Boston, MA: Springer.

Lihua Cao, D. Z. S. J. (2011). Pharmacological action, pharmacokinetics and clinical application of selective COX-2 inhibitor meloxicam. *Livestock and Veterinary*, *43*(7), 000100–000104.

Louder, A. M., Joshi, A. V., Ball, A. T., Cappelleri, J. C., Deminski, M. C., & Sanchez, R. J. (2011). Impact of Celecoxib restrictions in medicare beneficiaries with arthritis. *The American Journal of Managed Care*, *17*(7), 503–512.

Mainau, E., & Manteca, X. (2011). Pain and discomfort caused by parturition in cows and sows. *Applied Animal Behaviour Science*, *135*(3), 241–251. https://doi.org/10.1016/j.applanim.2011.10.020

Moberg, G. P. (2000). Biological response to stress: Implications for animal welfare. *The Biology of Animal Stress*, *1*, 21.

Moeremans, I., Devreese, M., De Baere, S., Croubels, S., & Hermans, K. (2019). Pharmacokinetics and absolute oral bioavailability of meloxicam in guinea pigs (*Cavia porcellus*). *Veterinary Anaesthesia and Analgesia*, *46*(4), 548–555. https://doi.org/10.1016/j.vaa.2018.11.011

Naidu, N. B., Chowdary, K., Murthy, K., Satyanarayana, V., Hayman, A., & Becket, G. (2004). Physicochemical characterization and dissolution properties of meloxicam–cyclodextrin binary systems. *Journal of Pharmaceutical and Biomedical Analysis*, *35*(1), 75–86. https://doi.org/10.1016/j.jpba.2004.01.003

Nguyen, T.-T.-L., Duong, V.-A., Maeng, H.-J., & Chi, S.-C. (2019). Development of an oil suspension containing granisetron hydrochloride as a sustained-release parenteral formulation for enhancement of pharmacokinetic properties. *Journal of Drug Delivery Science and Technology*, *51*, 643–650. https://doi.org/10.1016/j.jddst.2019.03.042

Pierre-Louis, T., & Cester, C. C. (2004). Pharmacokinetic-pharmacodynamic relationships and dose response to meloxicam in horses with induced arthritis in the right carpal joint. *American Journal of Veterinary Research*, *65*(11), 1533–1541.

Prunier, A., Mounier, A., & Hay, M. (2005). Effects of castration, tooth resection, or tail docking on plasma metabolites and stress hormones in young pigs. *Journal of Animal Science*, *83*(1), 216–222.

Rigato, H. M., Mendes, G. D., Borges, N. C. D. C., & Moreno, R. A. (2006). Meloxicam determination in human plasma by high-performance liquid chromatography coupled with tandem mass spectrometry

(LC-MS-MS) in Brazilian bioequivalence studies. *International Journal of Clinical Pharmacology and Therapeutics*, *44*(10), 489–498. https://doi.org/10.5414/CPP44489

Shukla, M., Singh, G., Sindhura, B. G., Telang, A. G., Rao, G. S., & Malik, J. K. (2007). Comparative plasma pharmacokinetics of meloxicam in sheep and goats following intravenous administration. *Comparative Biochemistry & Physiology Part C Toxicology & Pharmacology*, *145*(4), 528–532. https://doi.org/10.1016/j.cbpc.2007.01.020

Tang, S., Xiao, J., Guo, G., He, J., Hao, Z., & Xiao, X. (2010). Preparation of a newly formulated long-acting ceftiofur hydrochloride suspension and evaluation of its pharmacokinetics in pigs. *Journal of Veterinary Pharmacology & Therapeutics*, *33*(3), 238–245. https://doi.org/10.1111/j.1365-2885.2009.01126.x

Tian, Y., Wu, X., Zhang, M., Zhao, L., Xiong, Z., & Qin, F. (2018). Quantitative determination of meloxicam in dog plasma by high performance liquid chromatography-tandem mass spectrometry and its application in a pharmacokinetic study. *Biomedical Chromatography*, *32*(7), e4228. https://doi.org/10.1002/bmc.4228

Torrey, S., Devillers, N., Lessard, M., Farmer, C., & Widowski, T. (2009). Effect of age on the behavioral and physiological responses of piglets to tail docking and ear notching. *Journal of Animal Science*, *87*(5), 1778–1786.

Urayama, S., Tanaka, A., Kusano, K., Sato, H., Nagashima, T., Fukuda, I., … Matsuda, H. (2019). Oral administration of Meloxicam suppresses low-dose endotoxin challenge-induced pain in thoroughbred horses. *Journal of Equine Veterinary Science*, *77*, 139–143. https://doi.org/10.1016/j.jevs.2019.03.001

Uzun, B., Atli, O., Perk, B. O., Burukoglu, D., & Ilgin, S. (2015). Evaluation of the reproductive toxicity of naproxen sodium and meloxicam in male rats. *Human and Experimental Toxicology*, *34*(4), 415–429. https://doi.org/10.1177/0960327114542886

Von Borell, E., Baumgartner, J., Giersing, M., Jäggin, N., Prunier, A., Tuyttens, F., & Edwards, S. (2009). Animal welfare implications of surgical castration and its alternatives in pigs. *Animal*, *3*(11), 1488–1496. https://doi.org/10.1017/S1751731109004728

Wani, A. R., Roy, R. K., Ashraf, A., & Roy, D. C. (2013). Pharmacokinetic studies of meloxicam after its intravenous administration in local goat (*Capra hircus*) of Assam. *Veterinary World*, *6*(8), 516–520. https://doi.org/10.5455/vetworld.2013.516-520

Xide, T. U., & Zhu, J. (2002). *Pharmaceutics*. Beijing, China: People's Medical Publishing House.

Xiong, J., Zhu, Q., Lei, Z., Yang, S., Chen, P., Zhao, Y., … Qiu, Y. (2018). Bioequivalence evaluation of two 5% ceftiofur hydrochloride sterile suspension in pigs. *Journal of Veterinary Medical Science*, *80*(12), 1847–1852. https://doi.org/10.1292/jvms.18-0470

How to cite this article: Li Y, Guo F, Jiang X, et al. Pharmacokinetics and relative bioavailability of meloxicam oil suspension in pigs after intramuscular administration. *J vet Pharmacol Therap*. 2019;00:1–8. https://doi.org/10.1111/jvp.12826