3-6-2023

# Pharmacokinetics of intramuscular maropitant in pigs (Sus scrofa domesticus)

Joseph Smith
jsmit604@utk.edu

Jessica E. Gebert
*LMU*, jessica.gebert@lmunet.edu

Lisa S. Ebner
*LMU*, Lisa.Ebner@lmunet.edu

Kailee O. Bennett
*UTK*, kbenne32@vols.utk.edu

Rebecca J. Collins
*UTK*, rcolli36@vols.utk.edu

See next page for additional authors

Received: 19 October 2022 | Revised: 19 December 2022 | Accepted: 4 February 2023

DOI: 10.1111/jvp.13120

JOURNAL OF Veterinary Pharmacology and Therapeutics WILEY

PHARMACOKINETIC REPORT

# Pharmacokinetics of intramuscular maropitant in pigs (*Sus scrofa domesticus*)

Joe S. Smith[1,2] | Jessica E. Gebert[3] | Lisa S. Ebner[3] | Kailee O. Bennett[1] | Rebecca J. Collins[1] | Chiara E. Hampton[1] | Stephanie A. Kleine[4] | Pierre-Yves Mulon[1] | Christopher K. Smith[4] | Reza Seddighi[1] | Genevieve Bussieres[4] | Jonathan P. Mochel[2] | Heather K. Knych[5]

[1]Large Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee, USA

[2]Biomedical Sciences, College of Veterinary Medicine, Iowa State University, Ames, Iowa, USA

[3]College of Veterinary Medicine, Lincoln Memorial University, Harrogate, Tennessee, USA

[4]Small Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee, USA

[5]K. L. Maddy Equine Analytical Pharmacology Laboratory, School of Veterinary Medicine, University of California-Davis, Davis, California, USA

**Correspondence**
Joe S. Smith, Large Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee, USA.
Email: jss303@iastate.edu; jsmit604@utk.edu

## Abstract

Pigs are at risk of vomiting from medical conditions as well as the emetic side effects of drugs administered for peri-operative manipulations, but there is a lack of pharmacokinetic data for potential anti-emetic therapies, such as maropitant, in this species. The main objective of this study was to estimate plasma pharmacokinetic parameters for maropitant in pigs after a single intramuscular (IM) administration dosed at 1.0 mg/kg. A secondary objective was to estimate pilot pharmacokinetic parameters in pigs after oral (PO) administration at 2.0 mg/kg. Maropitant was administered to six commercial pigs at a dose of 1.0 mg/kg IM. Plasma samples were collected over 72 h. After a 7-day washout period, two pigs were administered maropitant at a dose of 2.0 mg/kg PO. Maropitant concentrations were measured via liquid chromatography/mass spectrometry (LC–MS/MS). A non-compartmental analysis was used to derive pharmacokinetics parameters. No adverse events were noted in any of the study pigs after administration. Following single IM administration, maximum plasma concentration was estimated at 412.7 ± 132.0 ng/mL and time to maximum concentration ranged from 0.083 to 1.0 h. Elimination half-life was estimated at 6.7 ± 1.28 h, and mean residence time was 6.1 ± 1.2 h. Volume of distribution after IM administration was 15.9 L/kg. Area under the curve was 1336 ± 132.0 h*ng/mL. The relative bioavailability of PO administration was noted to be 15.5% and 27.2% in the two pilot pigs. The maximum systemic concentration observed in the study pigs after IM administration was higher than what was observed after subcutaneous administration in dogs, cats, or rabbits. The achieved maximum concentration exceeded the concentrations for anti-emetic purposes in dogs and cats; however, a specific anti-emetic concentration is currently not known for pigs. Further research is needed into the pharmacodynamics of maropitant in pigs to determine specific therapeutic strategies for this drug.

KEYWORDS
anti-emetic, emesis, maropitant, nausea, neurokinin, porcine, swine, vomiting

  

## 1 | INTRODUCTION

Maropitant (IUPAC name: (2S,3S)-2-benzhydryl-N-[(5-tert-butyl-2-methoxyphenyl)methyl]-1-azabicyclo[2.2.2]octan-3-amine; Molecular formula: $C_{32}H_{40}N_2O$) is a synthetic neurokinin type-1 receptor antagonist which inhibits the central effect of the neurotransmitter Substance P. In veterinary medicine, maropitant is widely used in dogs for its anti-emetic activity (Benchaoui, Cox, et al., 2007). Specific conditions associated with emesis that can be prevented or managed by maropitant in dogs include chemotherapy (Benchaoui, Cox, et al., 2007), medical gastro-enteritis (de la Puente-Redondo et al., 2007), and motion sickness (Benchaoui, Siedek, et al., 2007), in addition to its use for prevention of peri-surgical emesis. Recently, maropitant has also been investigated for use in cats (Hay Kraus, 2017), rabbits (Ozawa et al., 2019), chickens (Mones et al., 2022), as well as horses (Berryhill et al., 2019, 2020).

Production and miniature companion pigs undergo many surgical procedures where inhibition of emesis would be beneficial for patient management (Anderson & Mulon, 2019; Smith & Seddighi, 2022). Miniature companion pigs are increasing in popularity as pets (Curnutte, 2014) and as such, will undergo anesthesia for routine procedures such as ovariohysterectomies (Cypher et al., 2017), tusk and hoof maintenance (Smith, Griffin, et al., 2022; Smith & Seddighi, 2022), as well as non-routine procedures such as gastrointestinal (Cain et al., 2020; Ehrle et al., 2019), urinary (Needleman & Videla, 2019), or orthopedic surgeries (Høy-Petersen et al., 2020; Smith et al., 2017). In addition, pigs will occasionally present to veterinarians for vomiting, and a paucity of information regarding the use of maropitant in pigs, including pharmacokinetics, currently exists. Descriptions of the use of maropitant in pigs are limited to case reports (Hobbs et al., 2021; Wheeler et al., 2020) and general recommendations (Mitek, 2017), with no data from prospective studies. The goal of this study was to report the pharmacokinetics (PK) of a single intramuscular dose of maropitant in pigs, as well as to perform a pilot evaluation of the PK of orally administered maropitant in pigs.

## 2 | MATERIALS AND METHODS

### 2.1 | Animals

Six healthy (5 gilts; 1 barrow) commercial breed-cross (Landrace x Yorkshire) pigs, 98–99 days of age and weighing 45.9 ± 2.5 kg, were evaluated. Pigs were housed in a climate-controlled facility with variable humidity and in individual pens. Pigs were fed a commercial swine feed (Co-op 16% Pig Grower Pellet, Tennessee Farmers Cooperative) twice a day and had ad libitum access to water. The diet met or exceeded the National Research Council recommendations for pigs. Prior to the implementation of the study, the pigs were examined for any clinical signs of disease or ill health and were excluded if noted. This project was approved by the University of Tennessee Institutional Animal Care and Use Committee (Protocol # 2897-0322).

### 2.2 | Sample collection

Maropitant citrate (Cerenia®, Zoetis Inc., Kalamazoo, MI, US) dosed at 1.0 mg/kg was injected in the left neck in accordance with Pork Quality Assurance guidelines with an 18 G 1.5-inch needle. Samples were collected from a previously implanted single lumen 20-cm 16 G catheter (LA1620-A; MILACATH, MILA International. Kentucky, US) that was surgically placed in the right jugular vein under general anesthesia. Catheter patency was maintained by daily flushing with 6 mL of NaCl 0.9% and locking with heparinized solution (100 IU/mL). Samples were collected at: 0 (prior to administration), 5, 10, 15, 30, and 45 min as well as 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 30, 36, 48, and 72 h after administration. For collection, the catheter was flushed with normal (0.9%) saline, and the push-pull technique (Hess & Decker, 2017) was utilized for blood collection, and the line was flushed with 10 mL heparinized saline afterwards. Once collected, the blood was immediately placed on ice and then centrifuged at 1500 ***g*** for 10 min. After centrifugation, the sample plasma was pipetted into individual cryovials. The plasma was stored at −80°C for analysis.

After a 7-day washout period, two pigs were used for pilot investigation of the PK parameters of oral maropitant. Pigs were dosed at 2.0 mg/kg, rounded up to the nearest half-tablet (Cerenia® Tablets, Zoetis Inc., Kalamazoo, MI, US) of the veterinary canine tablet formulation. The tablets were administered with peanut butter (not as a component of the offered pig feed) prior to morning feeding, with the amount of maropitant added to the peanut butter providing an internal exposure dose of 2 mg/kg. Sample collection time points were 0 (prior to administration), 15, and 30 min as well as 1, 1.5, 2, 4, 8, 12, 18, 24, 31, 48, and 72 h after administration. Pigs were monitored regularly for 72 h after administration for any adverse effect, as well as twice daily for an additional 96 h after the 72-h study period.

### 2.3 | Analytical chemistry

Sample extraction and concentration determination were conducted using a previously published method for equine plasma (Berryhill et al., 2019, 2020). Analysis was performed with a TSQ Vantage triple quadrupole mass spectrometer (MS) equipped with an ESI source (Thermo Scientific, San Jose, CA) (Berryhill et al., 2019). That was coupled with an 1100 LC system (Agilent Technologies, Palo Alto, CA) (Berryhill et al., 2019). After extraction, samples (30 μL) were separated on a C18 column (ACE C18, 2.1 × 00 mm, 3 μ ps; Mac-Mod Analytical, Chadds Ford, PA) and kept at 30°C (Berryhill et al., 2019). For this analysis, gradient mobile phase consisted of component A: water and 0.2% formic acid and B: 0.1% formic acid in acetonitrile at a flow rate of 0.35 mL/min (Berryhill et al., 2019). As previously reported for horses, in the MS/MS analysis, protonated molecular ions were isolated and fragmented using helium gas collision in the Q2 region with collision energy of 45 eV (maropitant) and 30 eV (d4-buprenorphine) (Berryhill et al., 2019). As previously developed

for horses, the resulting mass spectra were acquired using selective reaction monitoring mode, m/z 469.3→119.1 (maropitant) and m/z 472.3→101.1, 187 (d4-buprenorphine) (Berryhill et al., 2019). Calibration curves were generated with Quanbrowser software (Thermo Scientific, San Jose, CA), which was also used to generate quantitate analytes in samples by linear regression analysis (Berryhill et al., 2019). For the calibration curves, a weighting factor of 1/X was utilized. A partial validation was performed with pig plasma.

### 2.4 | Pharmacokinetic analysis

A non-compartmental approach for extravascular administration of maropitant in plasma was performed for each pig using commercially available pharmacokinetic software (PKanalix, Monolix Suite 2021R1, Lixoft, France). Maximum concentration ($C_{max}$) and time to maximum concentration ($T_{max}$) were taken directly from observation of the data. Analysis utilized the raw data, with expression based on statistical moments theory, and standard formulas for extravascular injection as follows:

1. Area under the maropitant concentration–time curve, extrapolated to infinity, $AUC_{inf}$.
2. Area under the moment curve, $AUMC_{inf}$.
3. Maropitant mean residence time, $MRT = AUMC_{inf}/AUC_{inf}$.
4. Maropitant elimination rate, $\lambda z$.
5. Maropitant terminal half-life, $T_{1/2}(\lambda z) = \ln(2)/\lambda z$.
6. Volume of distribution accounting for bioavailability, $V_Z/F$.

The linear/trapezoidal linear/log rule was used for data analysis to estimate the areas under the maropitant time-curves. Summary statistics were performed thereafter to derive the geometric mean and (min–max) range of the individual pharmacokinetic parameters. The pilot oral administration was reported as described above with reporting done for the individual animal. Additionally, relative bioavailability ($F_R$) was determined on two pigs by the following formula:

$$F(\text{Relative}) = \frac{\text{AUC(PO)}}{\text{AUC(IM)}} * \frac{\text{Dose(IM)}}{\text{Dose(PO)}}$$

## 3 | RESULTS

### 3.1 | Animals

No adverse effects were observed in any study animals, and the injection appeared well-tolerated by the pigs that were being fed during administration. One pig's catheter lost patency prior to the 48-h sampling timepoint (note: catheters were placed in the opposite side of the neck from where the IM injection was administered, and this loss of patency is likely unrelated to the injection). These two timepoints (48 and 72 h) were excluded from the pharmacokinetic analysis for this pig. Similarly, no adverse effects were noted in the two pigs administered the oral tablets of maropitant.

### 3.2 | Analytical chemistry

The response for maropitant was linear, with correlation coefficients of 0.99. The method was fully validated in a previous study including assessment of susceptibility to interference, specificity, accuracy, precision, limit of detection, and limit of quantification. As the method was validated previously for equine samples, a partial validation, including determination of intra-day precision and accuracy and the limit of detection and quantification, was conducted. Precision and accuracy of the assay were determined by assaying quality control samples (0.3, 20, and 600 ng/mL) in replicates ($n = 6$). Accuracy was 100%, 111%, and 99% for 0.3, 20, and 600 ng/mL, respectively. Precision was 14%, 7%, and 8% for 0.3, 20, and 600 ng/mL, respectively. The limit of quantitation was 0.1 ng/mL and the limit of detection was 0.05 ng/mL.

### 3.3 | Pharmacokinetics

The time versus concentration curve for maropitant after intramuscular injection is displayed in Figure 1. The PK parameters for maropitant after intramuscular injection are presented in Table 1. All pigs had detectable plasma concentrations of maropitant, including at the last sampling time point. The individual time versus concentration curves for the two pigs administered maropitant orally, as well as their individual concentration curves after intramuscular administration are presented in Figure 2. The individual PK parameters for these pigs after oral administration are presented in Table 2. The relative bioavailability of PO to IM administration in each pig was estimated at 15.5% (pig 1) and 27.2% (pig 2).

## 4 | DISCUSSION

In this study, the PK of maropitant citrate (1 mg/kg, IM) after single administration was determined for pigs. Although empirical use

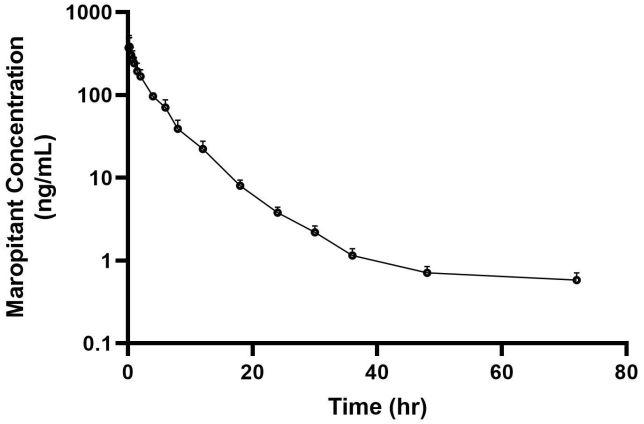


FIGURE 1 Mean plasma maropitant concentration (logarithmic scale) vs time (hr) profile for pigs ($n = 6$) administered a single dose (1.0 mg/kg) of maropitant via intramuscular injection. Mean is represented by an open circle with error bars.

| Parameter | Unit | Mean (±SD) | Minimum | Maximum |
|---|---|---|---|---|
| $C_{max}$ | ng/mL | 412.7 ±1.42 | 283.3 | 597.3 |
| $T_{max}$ | h | 0.2 ±2.52 | 0.083 | 1.0 |
| $AUC_{inf}$ | h*ng/mL | 1336 ±1.11 | 1090.0 | 1524.0 |
| $AUMC_{inf}$ | $h^2$*ng/mL | 9847 ±1.4 | 6667 | 17,321 |
| MRT | h | 6.1 ±1.2 | 5.3 | 7.15 |
| $\lambda z$ | 1/h | 0.047 ±0.028 | 0.077 | 0.15 |
| $T_{1/2}\ \lambda z$[a] | h | 6.6 ±1.3 | 4.7 | 9.0 |
| Cl/F | L/h/kg | 0.75 ±0.00002 | 0.67 | 0.84 |
| $V_Z/F$ | L/kg | 15.9 ±2.88 | 6.0 | 81.4 |

Abbreviations: $AUC_{inf}$, Area under the curve extrapolated to infinity; $AUMC_{inf}$, Area under the moments curve extrapolated to infinity; $C_{max}$, Maximum plasma concentration; MRT, Mean residence time; $T_{1/2}\ \lambda z$, Elimination half-life; $T_{max}$, Time to maximum plasma concentration; $V_Z/F$, (Apparent) Volume of distribution for extravascular administration; $\lambda z$, Elimination rate.

[a]Harmonic mean.

**TABLE 1** Pharmacokinetic parameters (mean ± SD; geometric unless indicated otherwise) in pigs following a single intramuscular injection of 1.0 mg/kg maropitant ($n = 6$).

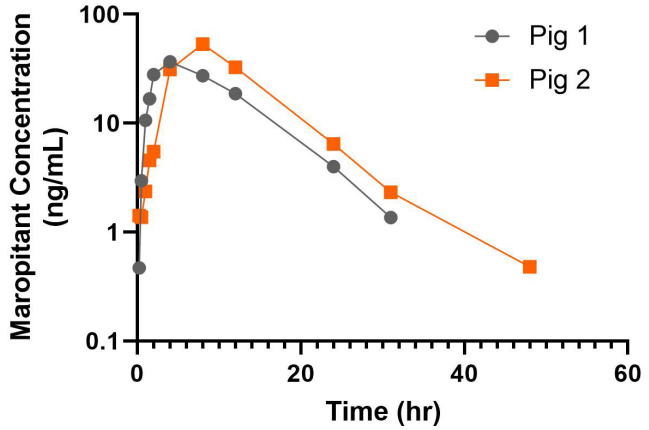


**FIGURE 2** Plasma maropitant concentrations (logarithmic scale) vs time (hr) profile for individual pigs ($n = 2$) administered a single dose (2.0 mg/kg) of maropitant orally. For this pilot investigation, pig 1 is identified with smokey gray circles and pig 2 is identified with volunteer orange squares.

**TABLE 2** Pilot pharmacokinetic parameters (individual values) in pigs following a single oral administration of 2.0 mg/kg maropitant ($n = 2$).

| Parameter | Unit | Pig 1 | Pig 2 |
|---|---|---|---|
| $C_{max}$ | ng/mL | 36.7 | 53.3 |
| $T_{max}$ | h | 4 | 8 |
| $AUC_{inf}$ | h*ng/mL | 417.4 | 676.4 |
| $AUMC_{inf}$ | $h^2$*ng/mL | 4635.3 | 7994.8 |
| MRT | h | 9.8 | 11.8 |
| $\lambda z$ | 1/h | 0.14 | 0.12 |
| $T_{1/2}\ \lambda z$ | h | 5.06 | 5.92 |
| $V_Z/F$ | L/kg | 31.7 | 25.8 |
| $F_R$ | % | 15.5 | 27.2 |

Abbreviations: $AUC_{inf}$, Area under the curve extrapolated to infinity; $AUMC_{inf}$, Area under the moments curve extrapolated to infinity; $C_{max}$, Maximum plasma concentration; $F_R$, Relative bioavailability; $T_{1/2}\ \lambda z$, Elimination half-life; MRT, Mean residence time; $T_{max}$, Time to maximum plasma concentration; $V_Z/F$, (Apparent) Volume of distribution for extravascular administration; $\lambda z$, Elimination rate.

of the drug has been described in clinical practice, to the author's knowledge no prospective studies in pigs currently exist for the PK of this drug in swine.

Vomiting in swine differs from other species in that it is commonly associated with infectious disease such as Transmissible Gastroenteritis, Porcine Epidemic Diarrhea virus, as well as toxins such as deoxynivalenol (Prelusky & Trenholm, 1993). The pathophysiology of vomiting in pigs is thought to be more responsive to action on serotonin ($5HT_3$) receptors via antagonists, than action on $5HT_2$ receptors (Prelusky & Trenholm, 1993). Antihistamine and antidopaminergic antiemetics were shown in that same study to not be effective in swine. Maropitant antagonizes neurokinin-1 receptors in the emetic center of the brain, known as the nucleus tractus solitarius (Riviere & Papich, 2018). Maropitant is considered a "broad spectrum" antiemetic because it blocks input from multiple sources via its action at this center, as opposed to other anti-emetic drugs which act on specific sources that provide input to the center (Riviere & Papich, 2018).

The maximum concentration ($C_{max}$) observed in the study pigs after intramuscular administration (412 ng/mL) was higher than observed after subcutaneous administration (1 mg/kg) in dogs, cats, or rabbits (Benchaoui, Cox, et al., 2007; Hickman et al., 2008; Ozawa et al., 2019). While an effective anti-emetic concentration for pigs is not known, this level exceeded the concentrations that are thought to be clinically effective in dogs (Benchaoui, Cox, et al., 2007; Hay Kraus, 2017). The time to maximum concentration ($T_{max}$) after intramuscular injection in the study pigs (0.2 h) was faster than observed for subcutaneous injection in dogs, cats, or rabbits (Benchaoui, Cox, et al., 2007; Hickman et al., 2008; Ozawa et al., 2019). This is expected as the more perfused nature of muscle typically allows for more rapid absorption than subcutaneous injections. Total exposure to maropitant after intramuscular injection, described as area under the curve extrapolated to infinity ($AUC_{inf}$), was greater than observed values in dogs, cats, or rabbits after subcutaneous

**TABLE 3** Comparative pharmacokinetics of maropitant citrate after extravascular injection in several domestic species.

| Species | Dose (mg/kg) | Route | $C_{max}$ (ng/mL) | $T_{max}$ (h) | Elimination half-life (h) | AUC (ng*h/mL) | References |
|---|---|---|---|---|---|---|---|
| Dogs | 1.0 | SC | 92 | 0.75 | 7.75 | 860 | Benchaoui, Cox, et al. (2007); Benchaoui, Siedek, et al. (2007) |
| Cats | 1.0 | SC | 269 | 0.5–2.0 (range) | 17.1 | Not reported | Hickman et al. (2008) |
| Rabbits | 1.0 | SC | 14.4 | 1.25 | 13.1 | 208.5 | Ozawa et al. (2019) |
| Pigs | 1.0 | IM | 412.7 | 0.2 | 6.6 | 1336 | Present Study |

Abbreviations: AUC, Area under the curve; $C_{max}$, Maximum plasma concentration; IM, Intramuscular administration; SC, Subcutaneous administration; $T_{max}$, Time to maximum plasma concentration.

injection (Benchaoui, Cox, et al., 2007; Hickman et al., 2008; Ozawa et al., 2019). Due to the differences in administration, it is uncertain at this time whether these differences in PK are due to species bioavailability. However, due to the lack of a true SC space in pigs, IM administration was chosen for the purpose of practicality. Volume of distribution after extravascular administration ($V_Z/F$) was high (15.9 L/kg) compared with reported values after IV administration in horses (6.54 L/kg) (Berryhill et al., 2019) and rabbits (3.5) (Ozawa et al., 2019); Table 3 displays comparative PK of maropitant after extravascular injection in multiple domestic species.

The maximum concentrations achieved after oral administration in the two pilot pigs (36.7 and 53.3 ng/mL) were less than the maximum concentrations observed in horses after oral administration (73.5 ng/mL) (Berryhill et al., 2020), although that study utilized a 4 mg/kg dose, and these values would be similar after dose correction. The terminal elimination half-life observed in the two pigs administered oral maropitant in this study was of 4.7 and 9 h, which was shorter than the 11.6 h reported in horses (Berryhill et al., 2020), but similar to reported in dogs (4.03 h after PO administration at 2.0 mg/kg; Benchaoui, Cox, et al., 2007). While our study evaluated the relative bioavailability ($F_R$) of PO administration when compared to IM, it should be noted that absolute bioavailability values (comparison of SC extravascular administration to IV administration; F) observed in dogs (23.7%) are also low, although these were less than the F (50%) noted in cats (Hickman et al., 2008). As the oral administration results we present are pilot data based on 2 pigs, the oral parameters of maropitant in pigs should be interpreted with caution until more studies are conducted.

Common adverse reactions to maropitant administration in other species include injection site reactions and excitation (Ozawa et al., 2019). These were not observed in our sample of pigs. It is possible that the lack of notable injection site reactions was due to the length of the needle used (1.5 inches to insure administration in muscle). Given the apparent absence of injection site reactions after IM injection in the studied pigs, this route could be considered in other species, such as rabbits where reactions were observed after subcutaneous administration (Ozawa et al., 2019). No feed refusal was noted at any point of the study period.

This work has the potential for multiple future applications. Studies investigating the pharmacodynamics, the complete PK of single and multiple dosing of the oral formulation, and IV administered maropitant will aid clinicians in better clinical use of this drug. In dogs, one trial evaluated the administration of maropitant or morphine prior to surgery, and in that study maropitant-administrated animals were significantly more likely to eat 3 h postoperatively (Marquez et al., 2015) compared with dogs treated with morphine pre-anesthetically, and this resumption of appetite could be utilized for both production and companion pigs undergoing anesthetic procedures. Similarly, maropitant led to improved anesthetic recoveries in dogs (Ramsey et al., 2014). Therefore, future studies should investigate the effects on the peri-anesthetic period in pigs, including effect of the route of administration on the clinical timeline to resolution of anti-emetic activity. As pigs of all types are a major food animal species in the United States (Smith, Merkatoris, et al., 2022), future studies should investigate the tissue depletion of maropitant in pigs to determine withdrawal recommendations. Non-linear mixed effect (NLME) analysis could be utilized in future studies to capture population variability of maropitant in pigs (Bon et al., 2018). Future studies could also investigate the PK of maropitant in miniature companion pig breeds, as it is currently unknown whether PK properties are conserved when compared to production pig breeds, as investigated in this study. Finally, the effects of multiple drug administration should be investigated to determine any drug–drug interactions from maropitant concurrent administration with anesthetic agents.

Limitations of this study include the small sample size and fairly homogenous patient population. While study populations of 4–6 animals are generally considered adequate for veterinary PK studies (Riviere & Chittenden, 2011), a sample size of this number is not adequate to capture all of the variability within a population. Another limitation is the loss of patency of one catheter at the later stages of sample collection in one pig. Comparison of PK parameters from other species is meant to be interpreted in a descriptive fashion, as robust statistical comparison of parameters cannot be done as the methods for each study vary in timelines as well as laboratories performing analytical chemistry analysis.

In conclusion, intramuscular maropitant citrate administered at 1.0 mg/kg to pigs achieves higher concentrations in a shorter period of time than observed for subcutaneous injection in dogs, cats, or rabbits. Intramuscular injections seemed well tolerated by the subject pigs without clinically noticeable side effects. Pilot

investigation of orally administered maropitant demonstrated lower maximum concentrations and a lower relative bioavailability compared with the intramuscular route. Future research is warranted in the pharmacodynamics of maropitant to allow for precision use for clinical situations where an anti-emetic would be ideal in porcine patients.

## AUTHOR CONTRIBUTIONS

JS, JG, LE, KB, and JM contributed to study design. JS, JG, LE, KB, RC, CH, SK, CS, GB, PYM, and RS contributed to study implementation. HK developed the analytical method and performed analysis of the samples. JS and JG performed the PK analysis. All authors contributed to manuscript construction.

## ETHICAL APPROVAL

All aspects of this study were approved by the University of Tennessee's Institutional Animal Care and Use Committee.

## ACKNOWLEDGMENTS

The authors wish to acknowledge Olivia Escher and Lainey Harvill for their assistance in sample collection as well as Christopher Brandon Lemons, Lucy Vanecek, Skylar Michael, and Alex Anderson for their contributions to pig husbandry.

## FUNDING INFORMATION

The authors wish to acknowledge the University of Tennessee, College of Veterinary Medicine's COE program for partial funding of this project.

## CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ANIMAL WELFARE STATEMENT

This project was approved by the University of Tennessee Institutional Animal Care and Use Committee (Protocol # 2897-0322). The authors confirm that this study met US Animal Welfare guidelines for such work.

## ORCID

*Joe S. Smith* https://orcid.org/0000-0002-4288-2262
*Stephanie A. Kleine* https://orcid.org/0000-0002-2432-7492
*Jonathan P. Mochel* https://orcid.org/0000-0002-0997-3111
*Heather K. Knych* https://orcid.org/0000-0002-8676-4970

## REFERENCES

Anderson, D. E., & Mulon, P. Y. (2019). Anesthesia and surgical procedures in swine. In J. J. Zimmerman, L. A. Karriker, A. Ramirez, K. J. Schwartz, G. W. Stevenson, & J. Zhang (Eds.), *Diseases of Swine* (pp. 171–196). Wiley.

Benchaoui, H. A., Cox, S. R., Schneider, R. P., Boucher, J. F., & Clemence, R. G. (2007). The pharmacokinetics of maropitant, a novel neurokinin type-1 receptor antagonist, in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *30*(4), 336–344. https://doi.org/10.1111/j.1365-2885.2007.00877.x

Benchaoui, H. A., Siedek, E. M., De La Puente-Redondo, V. A., Tilt, N., Rowan, T. G., & Clemence, R. G. (2007). Efficacy of maropitant for preventing vomiting associated with motion sickness in dogs. *Veterinary Record*, *161*(13), 444–447. https://doi.org/10.1136/vr.161.13.444

Berryhill, E. H., Knych, H., Chigerwe, M., Edman, J., & Magdesian, K. G. (2020). Pharmacokinetics of maropitant citrate after oral administration of multiple doses in adult horses. *Journal of Veterinary Pharmacology and Therapeutics*, *43*(3), 282–287. https://doi.org/10.1111/jvp.12844

Berryhill, E. H., Knych, H., Edman, J. M., & Magdesian, K. G. (2019). Pharmacokinetics of single doses of maropitant citrate in adult horses. *Journal of Veterinary Pharmacology and Therapeutics*, *42*(4), 487–491. https://doi.org/10.1111/jvp.12768

Bon, C., Toutain, P. L., Concordet, D., Gehring, R., Martin-Jimenez, T., Smith, J., Pelligand, L., Martinez, M., Whittem, T., Riviere, J. E., & Mochel, J. P. (2018). Mathematical modeling and simulation in animal health. Part III: Using nonlinear mixed-effects to characterize and quantify variability in drug pharmacokinetics. *Journal of Veterinary Pharmacology and Therapeutics*, *41*(2), 171–183. https://doi.org/10.1111/jvp.12473

Cain, A., Kirkpatrick, J., & Breuer, R. (2020). A case of a linear foreign body removal in a miniature companion pig. *Journal of Dairy, Veterinary & Animal Research*, *9*(1), 6–9.

Curnutte, M. (2014). *The big problem with mini-pigs*. National Geographic.

Cypher, E., Videla, R., Pierce, R., Snowden, R. T., Sexton, J. A., & van Amstel, S. (2017). Clinical prevalence and associated intraoperative surgical complications of reproductive tract lesions in pot-bellied pigs undergoing ovariohysterectomy: 298 cases (2006–2016). *The Veterinary Record*, *181*(25), 685. https://doi.org/10.1136/vr.104294

de la Puente-Redondo, V. A., Siedek, E. M., Benchaoui, H. A., Tilt, N., Rowan, T. G., & Clemence, R. G. (2007). The anti-emetic efficacy of maropitant (Cerenia) in the treatment of ongoing emesis caused by a wide range of underlying clinical aetiologies in canine patients in Europe. *The Journal of Small Animal Practice*, *48*(2), 93–98. https://doi.org/10.1111/j.1748-5827.2006.00321.x

Ehrle, A., Gillespie, A., & Rubio-Martinez, L. M. (2019). Management of a linear foreign body gastrointestinal obstruction in a miniature pig. *Veterinary Record Case Reports*, *7*(3), e000791. https://doi.org/10.1136/vetreccr-2018-000791

Hay Kraus, B. L. (2017). Spotlight on the perioperative use of maropitant citrate. *Veterinary Medicine (Auckland)*, *8*, 41–51. https://doi.org/10.2147/vmrr.S126469

Hess, S., & Decker, M. (2017). Comparison of the single-syringe push-pull technique with the discard technique for obtaining blood samples from pediatric central venous access devices. *Journal of Pediatric Oncology Nursing*, *34*(6), 381–386. https://doi.org/10.1177/1043454217713453

Hickman, M. A., Cox, S. R., Mahabir, S., Miskell, C., Lin, J., Bunger, A., & McCall, R. B. (2008). Safety, pharmacokinetics and use of the novel NK-1 receptor antagonist maropitant (Cerenia™) for the prevention of emesis and motion sickness in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *31*(3), 220–229. https://doi.org/10.1111/j.1365-2885.2008.00952.x

Hobbs, K. J., DeNotta, S. L., Gallastegui, A., Elane, G. L., Rivero, L. A., Adkins, P., & Gomez, D. E. (2021). Obstipation in pet pigs: 24 cases. *The Canadian Veterinary Journal*, *62*(8), 843–848.

Høy-Petersen, J., Smith, J. S., Merkatoris, P. T., Black, K. E., Faivre, C. M., Miles, K. G., Tatarniuk, D. M., & Kraus, K. H. (2020). Case

report: Trochlear wedge sulcoplasty, tibial tuberosity transposition, and lateral imbrication for correction of a traumatic patellar luxation in a miniature companion pig: A case report and visual description. *Frontiers in Veterinary Science*, *7*(1166), 1–9. https://doi.org/10.3389/fvets.2020.567886

Marquez, M., Boscan, P., Weir, H., Vogel, P., & Twedt, D. C. (2015). Comparison of NK-1 receptor antagonist (Maropitant) to morphine as a pre-anaesthetic agent for canine ovariohysterectomy. *PLoS One*, *10*(10), e0140734. https://doi.org/10.1371/journal.pone.0140734

Mitek, A. (2017). *Pot-bellied pig sedation*. Fast Facts and Drug Protocols. https://vetmed.illinois.edu/pot-bellied-pig-sedation-fast-facts-drug-protocols/

Mones, A. B., Petritz, O. A., Knych, H. K., Sadar, M. J., Thomson, A. E., & Guzman, D. S. (2022). Pharmacokinetics of maropitant citrate in Rhode Island red chickens (*Gallus gallus* domesticus) following subcutaneous administration. *Journal of Veterinary Pharmacology and Therapeutics*, *45*, 495–500. https://doi.org/10.1111/jvp.13082

Needleman, A., & Videla, R. (2019). Urolithiasis in a female miniature potbellied pig. *Veterinary Record Case Reports*, *7*(3), e000809. https://doi.org/10.1136/vetreccr-2018-000809

Ozawa, S. M., Hawkins, M. G., Drazenovich, T. L., Kass, P. H., & Knych, H. K. (2019). Pharmacokinetics of maropitant citrate in New Zealand white rabbits (*Oryctolagus cuniculus*). *American Journal of Veterinary Research*, *80*(10), 963–968. https://doi.org/10.2460/ajvr.80.10.963

Prelusky, D. B., & Trenholm, H. L. (1993). The efficacy of various classes of anti-emetics in preventing deoxynivalenol-induced vomiting in swine. *Natural Toxins*, *1*(5), 296–302. https://doi.org/10.1002/nt.2620010508

Ramsey, D., Fleck, T., Berg, T., Nederveld, S., DeLong, D., Tena, J.-K., Aleo, M., & McCall, R. (2014). Cerenia prevents perioperative nausea and vomiting and improves recovery in dogs undergoing routine surgery. *International Journal of Applied Research in Veterinary Medicine*, *12*(3), 228–237.

Riviere, J. E., & Chittenden, J. (2011). Study design and data analysis. In J. E. Riviere (Ed.), *Comparative pharmacokinetics* (2nd ed., p. 311). Wiley.

Riviere, J. E., & Papich, M. G. (2018). *Veterinary pharmacology and therapeutics*. John Wiley & Sons.

Smith, J., Griffin, C., Jones, P., Mulherin, B. L., & Hecht, S. (2022). Severe mandibular osteomyelitis and exfoliation of a mandibular canine tooth in a Vietnamese potbellied pig. *Veterinary Record Case Reports*, *10*(2), e348. https://doi.org/10.1002/vrc2.348

Smith, J., Merkatoris, P., Breuer, R. M., Videla, R., Mulon, P.-Y., Schleining, J., Nagy, D., Fajt, V., Reed, S., Mochel, J. P., Kreuder, A., & Dowling, P. (2022). Letter regarding "gastrointestinal foreign bodies in pet pigs: 17 cases". *Journal of Veterinary Internal Medicine*, *36*(4), 1199–1200. https://doi.org/10.1111/jvim.16479

Smith, J. S., Chigerwe, M., Kanipe, C., & Gray, S. (2017). Femoral head ostectomy for the treatment of acetabular fracture and coxofemoral joint luxation in a potbelly pig. *Veterinary Surgery*, *46*(2), 316–321. https://doi.org/10.1111/vsu.12604

Smith, J. S., & Seddighi, R. (2022). Miniature companion pig sedation and anesthesia. *The Veterinary Clinics of North America. Exotic Animal Practice*, *25*(1), 297–319. https://doi.org/10.1016/j.cvex.2021.08.007

Wheeler, E. P., Abelson, A. L., Wetmore, L. A., Jenei, T. M., & Rozanski, E. A. (2020). Anesthesia case of the month. *Journal of the American Veterinary Medical Association*, *257*(8), 809–812. https://doi.org/10.2460/javma.257.8.809

**How to cite this article:** Smith, J. S., Gebert, J. E., Ebner, L. S., Bennett, K. O., Collins, R. J., Hampton, C. E., Kleine, S. A., Mulon, P.-Y., Smith, C. K., Seddighi, R., Bussieres, G., Mochel, J. P., & Knych, H. K. (2023). Pharmacokinetics of intramuscular maropitant in pigs (*Sus scrofa domesticus*). *Journal of Veterinary Pharmacology and Therapeutics*, *00*, 1–7. https://doi.org/10.1111/jvp.13120