ORIGINAL ARTICLE

Pharmacokinetics of maropitant citrate in Rhode Island Red chickens (*Gallus gallus domesticus*) following subcutaneous administration

Alissa B. Mones[1] | Olivia A. Petritz[1] | Heather K. Knych[2,3] | Miranda J. Sadar[4] | Andrea E. Thomson[1] | David Sanchez-Migallon Guzman[5]

[1]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, USA

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

[3]Department of Veterinary Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, California, USA

[4]Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Ft. Collins, Colorado, USA

[5]Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California, USA

Correspondence
Olivia A. Petritz, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1060 William Moore Drive, Raleigh, 27607, NC, USA.
Email: oapetrit@ncsu.edu

Abstract

Maropitant citrate is a synthetic neurokinin-1 receptor antagonist and substance P inhibitor used for control of emesis in dogs in cats. Maropitant citrate is used empirically in birds, despite a lack of pharmacokinetic data in avian species. The objective of this study was to determine the pharmacokinetic profile of a single dose of maropitant citrate 1 and 2 mg/kg subcutaneously (SC) in eight Rhode Island Red hens (*Gallus gallus domesticus*). A crossover study design was used with 1-week washout between trials. Blood samples were collected over 36 h after drug administration. Plasma concentrations were measured using liquid chromatography–tandem mass spectrometry and pharmacokinetic parameters were determined via non-compartmental analysis. The mean maximum plasma concentration, time to maximum concentration, and elimination half-life following 1 and 2 mg/kg SC were 915.6 ± 312.8 ng/ml and 1195.2 ± 320.2 ng/ml, 0.49 ± 0.21 h and 1.6 ± 2.6 h, and 8.47 ± 2.24 h and 8.58 ± 2.6 h, respectively. Pharmacokinetic data suggests doses of 1 or 2 mg/kg SC may be administered every 12–24 h to maintain above target plasma concentration similar to dogs (90 ng/ml). These data provide a basis for further investigation of maropitant citrate pharmacokinetics and pharmacodynamics in birds.

KEYWORDS
antiemetic, avian, maropitant, neurokinin-1 agonist, substance P

1 | INTRODUCTION

Maropitant citrate is a synthetic neurokinin-1 (NK-1) receptor antagonist developed as an antiemetic for use in dogs (Benchaoui et al., 2007). The drug prevents emesis by selectively inhibiting the effect of substance P, a potent NK1 receptor agonist that is widely distributed both centrally and peripherally in the gastrointestinal tract (Diemunsch & Grélot, 2000; O'Connor et al., 2004; Sedlacek et al., 2008). The NK-1 receptor antagonists are the standard of care in human cancer patients to prevent emesis associated with

chemotherapy, and maropitant citrate is commonly administered clinically at 1 mg/kg intravenously (IV) or subcutaneously (SC) once daily for a broad range of emetic stimuli in dogs and cats (Benchaoui et al., 2007; De la Puente-Redondo et al., 2007; Hickman et al., 2008; Kraus, 2013; Martin-Flores et al., 2016; Ramsey et al., 2008; Rau et al., 2010; Trepanier, 2015; Vail et al., 2007). Maropitant citrate has also been investigated for anti-inflammatory, analgesic, and inhalant anesthesia sparing effects, related to the involvement of substance P in several other physiologic pathways (Boscan et al., 2011; Kinobe & Miyake, 2020; Niyom et al., 2013).

Regurgitation or vomiting is a common nonspecific clinical presentation for avian patients with proventriculitis/ventriculitis, coelomitis, gastrointestinal obstruction, neoplasia, toxin exposure, and other systemic diseases (Girling, 2004). Substance P-immunoreactive nerve components have been demonstrated within the central nervous system of the pigeon, a commonly used emetogenic animal model (Tanihata et al., 2003). Vofopitant (GR205171), an NK-1 receptor antagonist used in human medicine, has been shown to reduce the emetic response to cisplatin administered to pigeons, suggesting that NK-1 receptor antagonists may be useful as an antiemetic for avian patients (Tanihata et al., 2003).

Although maropitant citrate has been used empirically in birds at doses of 1 mg/kg SC and IM (Hawkins et al., 2017), there are no pharmacokinetic studies to support its use. The goal of this study was to determine the pharmacokinetic profile of maropitant citrate following a single subcutaneous dose in Rhode Island Red hens, a commonly kept breed of chicken in backyard flocks.

2 | MATERIALS AND METHODS

2.1 | Animal use statement

A pilot study was performed in four Rhode Island Red hens to collect preliminary data for design of the main study, consisting of eight additional Rhode Island Red chickens. All chickens were maintained in an indoor research flock at North Carolina State University College of Veterinary Medicine's Laboratory Animal Resources Facility. Hens for the pilot study ($n = 4$) averaged 2.21 kg (range 1.9–2.65 kg). Hens for the main study ($n = 8$) averaged 2.03 kg (range 1.7–2.45 kg). This protocol was approved by the North Carolina State University Institutional Animal Care and Use Committee (NC State IACUC #21–152).

2.2 | Animal care

All hens were 2.5 years old and deemed healthy based on a physical examination, packed cell volume/total solids, and a plasma biochemistry panel (VetScan Avian/Reptile Profile Plus, Abaxis, Inc, Union City, CA, USA) within 3 months prior to the start of the study. Individual plastic bands were placed around one pelvic limb on each bird for identification purposes. Birds were housed individually in 155 cm × 92 cm × 173 cm floor pens in a temperature-controlled room (75–78°F) on a 12-h light–dark cycle. Pens contained wood shaving litter and free choice access to water via bell poultry waterers. A fount feeder containing a pelleted maintenance layer diet (Purina Layena Pellets, Purina Animal Nutrition, Gray Summit, MO, USA) was placed in each pen 2 h after drug dosing and provided *ad libitum* between trials.

2.3 | Drug administration

Hens were weighed on the morning of the study and drug doses were calculated. At time 0 h, chickens in the pilot study received maropitant citrate (10 mg/ml, Cerenia, Zoetis, Kalamazoo, MI, USA; $C_{38}H_{50}N_2O$; (2 s, 3 s)-2-benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl)quinuclidin-3-amine; Chemical Abstracts Service 147,116–67-4) 2 or 10 mg/kg SC ($n = 2$ per dose). For the main study, randomization software (QuickCalcs 2018, GraphPad Software Inc., CA, USA) was used to assign chickens to receive maropitant citrate at 1 or 2 mg/kg SC. Maropitant citrate was administered SC over the right or left lateral thigh. A 25-gauge needle (3/8 inch) was directed beneath the skin and placement was confirmed by negative aspiration prior to drug administration. A skin marker was used to encircle the injection site for future monitoring of any potential injection site reactions (Skin-Skribe, HMS-Hospital Marketing Services, Naugatuck, CT, USA). Injection sites were visually evaluated at 24 h and 7 days post-injection. Following a 7-days washout period, each chicken received the opposite treatment. Investigators were not blinded to the treatment each chicken had received.

2.4 | Sample collection

Blood samples (0.3–0.6 ml) were collected from the metatarsal, ulnar, or jugular veins immediately before (time 0) and at predetermined time intervals after drug administration. Blank plasma was harvested from a separate population of Rhode Island Red chickens for generation of calibration curves and quality control samples. Samples for the pilot study were collected over a 48 h period (5, 10, 15, 30, and 45 min, and 1, 2, 4, 8, 12, 24, and 48 h). Based on the results of the pilot study blood samples for the main study were collected up to 36 h post-maropitant administration (10, 15, 30, 45 min and 1, 2, 4, 8, 12, 24, and 36 h). Blood samples were immediately transferred to a lithium heparin tube (BD Microtainer, Thermo Fisher Scientific Inc., Waltham, MA, USA) after collection and placed on ice. Over the course of the pilot and main study, the volume of blood removed from each chicken was less than 1% of the birds' total body weight, in accordance with the IACUC regulations.

2.5 | Sample processing

Samples were centrifuged at 3000 *g* for 5 min within an hour of collection. Plasma was harvested and frozen at −80°C in 2.0 ml cryovials

(CryoClear, Globe Scientific Inc, Mahwah, NJ, USA) until analysis of maropitant citrate concentrations.

2.6 | Determination of maropitant citrate concentrations

Plasma calibrators were prepared by dilution of the maropitant citrate working standard solutions (Toronto Research Chemicals, Toronto, ON, USA) with drug free chicken plasma to concentrations ranging from 0.1 to 5000 ng/ml. Calibration curves and negative control samples were prepared fresh for each quantitative assay. In addition, quality control samples (chicken plasma fortified with analyte at three concentrations within the standard curve) were included with each sample set as an additional check of accuracy.

Prior to analysis, 100 µl of plasma was diluted with 300 µl of acetonitrile (ACN):1 M acetic acid (9,1, v:v) containing 100 ng/ml of d4-buprenorphine internal standard (Cerilliant (Round Rock, TX), to precipitate proteins. The samples were vortexed on a Glas-Col Multi-Pulse Vortexer (Terre Haute, IN) for 1.5 min to mix, refrigerated for 20 min, vortexed for an additional 1 min, centrifuged in a Sorvall ST 40R centrifuge (Thermo Scientific, San Jose, CA, USA) at 4300 rpm/3830 g for 10 min at 4°C and 30 µl was injected into the liquid chromatography tandem mass spectrometry (LC–MS/MS) system.

The concentration of maropitant citrate was measured in plasma by LC–MS/MS. Quantitative analysis of plasma was performed on a TSQ Vantage triple quadrupole mass spectrometer (Thermo Scientific) having an 1100 series liquid chromatography system (Agilent Technologies, Palo Alto, CA). The system was operated using positive electrospray ionization [ESI (+)]. The spray voltage was set at 3500 V, sheath gas and auxillary gas were 45 and 30, respectively (arbitrary units), vaporizer temperature was 320°C, and capillary temperature was 300°C. Product masses and collision energies were optimized by infusing the standards into the mass spectrometer. Chromatography employed an ACE 3 C18 10 cm × 2.1 mm 3 µm column (Mac-Mod Analytical, Chadds Ford, PA, USA) and a linear gradient of acetonitrile (ACN) in water, with 0.2% formic acid, at a flow rate of 0.35 ml/min. The initial ACN concentration was held at 5% for 0.33 min, ramped to 99% over 5.5 min and held at that concentration for 0.33 min, before re-equilibrating for 3.75 min at initial conditions.

Detection and quantification was conducted using selective reaction monitoring (SRM) of initial precursor ion for maropitant citrate (mass to charge ratio [m/z] 469.3) and the internal standard d4-buprenorphine ([m/z] 472.3). The response for the product ions for maropitant citrate (m/z 167.1) and the internal standard d4-burprenorphine (m/z 101.1, 187) were plotted and peaks at the proper retention time were integrated using Quanbrowser software (Thermo Scientific). Quanbrowser software was used to generate calibration curves and quantitate analytes in all samples by linear regression analysis. A weighting factor of 1/X was used for all calibration curves.

The response for maropitant citrate was linear and gave a correlation coefficient of >0.99. Accuracy was reported as percent nominal concentration and precision was reported as percent relative standard deviation. For maropitant citrate, accuracy was 114% for 0.3 ng/ml, 110% for 20 ng/ml, and 115% for 600 ng/ml. Precision was 6% for 0.3 ng/ml, 3% for 20 ng/ml, and 5% for 600 ng/ml. The technique was optimized to provide a limit of quantitation of 0.1 ng/ml and a limit of detection of approximately 0.05 ng/ml for maropitant citrate.

2.7 | Pharmacokinetic analysis

The peak concentration (C_{max}) and time to peak plasma concentration (T_{max}) were determined by visual inspection of the concentration-time data. Non-compartmental analysis and a commercially available computer software program (Phoenix Winnonlin v8.0, Princeton, NJ) were used for determination of pharmacokinetic parameters. The area under the plasma concentration curve (AUC), slope of the terminal portion of the concentration time curve (lambda z), and terminal half-life (half-life lambda z) were determined. The area under curve (AUC) from time 0 to infinity ($AUC_{0 \to \infty}$) was determined using the linear up-log down trapezoidal rule.

3 | RESULTS

No adverse effects were observed following maropitant citrate 2 or 10 mg/kg SC during the pilot study. The C_{max} and T_{max} following 2 and 10 mg/kg SC were 1402.97 ng/ml at 1 h and 3680.52 ng/ml at 0.25 h respectively. Results of the pilot study were used to refine the dose administration strategy for the main study. Mean ± SD plasma concentration-time curves for maropitant citrate in chickens following subcutaneous administration of 1 and 2 mg/kg are depicted in Figure 1. Mean ± SD pharmacokinetic parameters for 1 and 2 mg/kg are presented in Table 1.

In the main study, 24 h following the 1 mg/kg SC dose, mild erythema was observed at 3/8 injection sites and moderate bruising was observed at 1/8 injection sites. Following administration of the 2 mg/kg SC dose, mild erythema was observed at 5/8 injection sites and moderate bruising was observed at 1/8 injection sites. At 7 days post injection, all injection site reactions had resolved aside from mild bruising in one 2 mg/kg SC dose. No other clinically appreciable abnormalities were present for the duration of the study.

4 | DISCUSSION

Results from this study indicate maropitant citrate 1 and 2 mg/kg SC were rapidly absorbed in chickens. The mean ± standard deviation T_{max} in chickens that received 1 mg/kg SC was 0.49 ± 0.21 h. This was faster than the T_{max} observed for the same dose in dogs (0.75 h), cats (0.5–2 h), and rabbits (1.25 h) (Benchaoui et al., 2007; Hickman

et al., 2008; Ozawa et al., 2019). The mean±standard deviation T_{max} in chickens following 2mg/kg SC was 1.6±2.6h, which was more consistent with observations in cats and rabbits that received 1mg/kg SC (Hickman et al., 2008, Ozawa et al., 2019). Rapid drug absorption following subcutaneous injections in birds is a common finding and may be attributed to a lack of substantial subcutaneous adipose tissue which allows more direct access to vascular absorption (Gleeson et al., 2018; Guzman et al., 2017).

The C_{max} following 1 and 2mg/kg SC were 915.6 and 1195.2ng/ml, respectively. The C_{max} following 1mg/kg was nearly 10 times higher than dogs (92ng/ml) and 3.4 times higher than cats (269ng/mL) when administered the same dose (Benchaoui et al., 2007; Hickman et al., 2008). Additionally, the observed C_{max} at the 1mg/kg SC dose in chickens was over 60-fold that observed in a study of the same dose in rabbits (14.4ng/ml), and four-fold the observed C_{max} for rabbits receiving 10mg/kg SC (231.7ng/ml) (Ozawa et al., 2019; Sadar et al., 2022). This was an unexpected finding, as many other drugs generally require higher dosing in avian species as a result of increases in metabolic rate compared to mammals (Dorrestein, 1991).
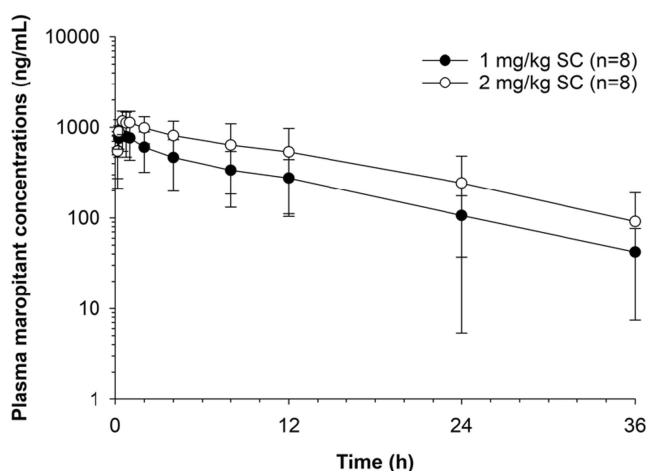

FIGURE 1 Plasma concentration (mean±standard deviation) time curve of maropitant citrate in Rhode Island Red hens (*Gallus gallus domesticus*) (*n* = 8) following SC administration of 1 and 2mg/kg doses

The C_{max} reached at both doses tested in the main study exceeded target concentrations in dogs for 12–24h (90ng/ml), although pharmacodynamic effects of maropitant in avian species have not yet been evaluated and the clinical significance of these results is unknown (Benchaoui et al., 2007; Boscan et al., 2011).

The plasma elimination half-life ($t_{1/2}$) in chickens receiving 1 and 2mg/kg SC (8.47h and 8.58h, respectively) was longer than dogs (7.75h), but shorter than cats (13–17h) and rabbits (13.1h) that received the same dose (Benchaoui et al., 2007; Hickman et al., 2008; Ozawa et al., 2019). The prolonged $t_{1/2}$ observed in chickens compared to dogs was unexpected, as most drugs have shorter half-lives in birds compared to mammals (Dorrestein, 1991). Extrapolation of doses between mammalian and avian species is complicated by several physiological and anatomical differences, including the avian renal portal system and a paucity of information regarding avian cytochrome P450 activity in avian drug metabolism (Hunter, 2010). In the avian renal portal system, venous blood from the gastrointestinal tract and pelvic region enters a ring of portal vessels and then either passes into the renal parenchyma and renal veins, and/or bypasses the kidney and returns to systemic venous circulation through the liver (Smith et al., 2000). Although renal elimination of maropitant in mammals is considered to generally be negligible with primary hepatic elimination, drugs injected in the caudofemoral region may be carried through the renal portal system, and a fraction of drug may be affected by renal excretion without reaching systemic circulation, or may bypass the kidneys and be influenced directly by hepatic circulation (Bello et al., 2022; Frazier et al., 1995). As a result, it is possible that SC injection over the thigh in this study may have influenced volume of distribution (Benchaoui et al., 2007). Additionally, the observed differences in plasma elimination half-life in this study may also be related to the extrapolation method required to calculate the terminal elimination rate constant (λ_z) at the 36h time point.

In comparing pharmacokinetic parameters between 1 and 2mg/kg SC doses in chickens, absorption and elimination appear to follow first order (linear) kinetics in this dose range. This is similar to the pharmacokinetics of maropitant in this dose range in cats, while the drug follows dose-dependent pharmacokinetics at higher dosages

TABLE 1 Non-compartmental pharmacokinetic parameters (mean±standard deviation) of maropitant citrate in Rhode Island Red hens (*Gallus gallus domesticus*) (*n* = 8) following SC administration of 1 and 2mg/kg doses

Parameter	Units	1mg/kg SC		2mg/kg SC	
		Mean	Standard deviation	Mean	Standard deviation
λ_z	1/h	0.08	0.02	0.08	0.02
$t_{1/2\lambda z}$	h	8.47	2.24	8.58	2.6
$AUC_{0\to\infty}$	h*ng/ml	8861.7	4524.9	15687.4	10713.7
%AUC_{extrap}	%	6.6	6.0	7.1	4.7
T_{max}	h	0.49	0.21	1.6	2.6
C_{max}	ng/ml	915.6	312.8	1195.2	320.2

Abbreviations: λ_z, terminal phase elimination rate constant; $t_{1/2\lambda z}$, terminal half life; $AUC_{0\to\infty}$, area-under-the-curve from time 0 to infinity; %AUC_{extrap}, percent of area under the curve extrapolated to infinity; C_{max}, peak concentration; T_{max}, time to peak concentration.

in dogs (Benchaoui et al., 2007; Hickman et al., 2008). Pilot data for hens that received 10 mg/kg maropitant citrate SC showed a C_{max} of 3469.42 ng/ml, which was approximately 3.7 times higher than the C_{max} observed in hens that received a 1 mg/kg dose. This was similar to dose-dependent pharmacokinetic observations in dogs, where doses of 1 and 8 mg/kg IV showed an increase in C_{max} of approximately 2.7 fold at the higher dose. (Benchaoui et al., 2007). Further evaluation of pharmacokinetic parameters of maropitant citrate in chickens and other avian species are required to develop a better understanding of absorption and elimination within different dose ranges in birds.

Injection site reactions ranging in severity from mild erythema to moderate bruising were observed within 24 h in 10/16 injections administered during the main study. Localized reactions at the subcutaneous injection site have also been reported in rabbits and dogs (Ozawa et al., 2019; Vail et al., 2007). Maropitant is known to cause discomfort and transient pain on injection in various mammalian species (De la Puente-Redondo et al., 2007; Martin-Flores et al., 2016). The discomfort associated with maropitant injection has been shown to be temperature dependent, and current recommendations are to keep maropitant cold (4°C refrigerated rather than 37°C room temperature) and inject it immediately to decrease the potential for injection pain and site reaction (Narishetty et al., 2009). Maropitant for this study was kept on ice until immediately prior to injection and chickens did not exhibit aversive behavior during subcutaneous drug administration, so the injections did not appear to cause immediate discomfort. It is possible that the high core body temperature of avian species may have resulted in rapid warming of the drug following the injection and subsequent inflammation and erythema or bruising at the injection site, although inflammatory effects of maropitant citrate have not previously been described (Nascimento et al., 2012). The temperature of maropitant citrate immediately prior to administration was not measured in this study, and the opposite possibility of the drug being colder than 4°C prior to injection could have contributed to the observed injection site reactions. No other adverse effects were observed, even following administration of 10 mg/kg SC doses to two hens during the pilot study. Additionally, the observed localized injection site reactions in this study resolved within 7 days for all but one injection site and no other appreciable negative clinical impacts occurred following drug administration.

This study provides the first pharmacokinetic analysis of an antiemetic medication in any avian species. This data supports anecdotal use of maropitant citrate 1 or 2 mg/kg SC in birds with a dosing frequency of every 12–24 h in Rhode Island Red hens. As with other medications, the potential exits for differences in drug absorption and similar pharmacokinetics should not be assumed across avian species or even between breeds of chickens (Souza et al., 2021).

Limitations of this study include a small sample size, use of only female chickens, evaluation of a single subcutaneous dosing route, and a limited course of time point sampling of only 36 h. Additionally, bioavailability and clearance of maropitant citrate could not be evaluated as an intravenous dose was not included in the study, and significant drug concentrations were still apparent at the 36 h

time point. Single dose administration also precludes evaluation of drug accumulation and toxicity, and the effects of repeated dosing remain unknown. Further studies investigating the pharmacokinetics of this medication in other species, evaluating other routes of administration (e.g. oral, intravenous), and performance of pharmacodynamic studies evaluating the potential for use as an anti-emetic, anti-inflammatory, analgesic, and minimum-alveolar-concentration sparing drug in birds are warranted.

5 | CONCLUSION

In conclusion, maropitant citrate 1 mg/kg SC every 12 h in Rhode Island Red hens achieves comparable plasma concentrations effective for prevention of emesis in dogs. Adverse effects were limited to mild to moderate transient injection site reactions. This is the first pharmacokinetic analysis of an antiemetic medication in birds, and provides data for further investigations of pharmacokinetic and pharmacodynamic studies of maropitant citrate in this, and other avian, species.

ORCID
Olivia A. Petritz https://orcid.org/0000-0003-2249-0904
Heather K. Knych https://orcid.org/0000-0002-8676-4970
Miranda J. Sadar https://orcid.org/0000-0002-3097-7432

REFERENCES

Bello, A., Poźniak, B., Smutkiewicz, A., & Świtała, M. (2022). The influence of the site of drug administration on florfenicol pharmacokinetics in turkeys. *Poult Sci J, 101*(1), 101536.

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. *J Vet Pharmacol, 30*(4), 336–344.

Boscan, P., Monnet, E., Mama, K., Twedt, D. C., Congdon, J., & Steffey, E. P. (2011). Effect of maropitant, a neurokinin 1 receptor antagonist, on anesthetic requirements during noxious visceral stimulation of the ovary in dogs. *Am J Vet Res, 72*(12), 1576–1579.

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. *J Small Anim Pract, 48*(2), 93–98.

Diemunsch, P., & Grélot, L. (2000). Potential of substance P antagonists as antiemetics. *Drugs, 60*, 533–546.

Dorrestein, G. M. (1991). The pharmacokinetics of avian therapeutics. *Vet Clin N Am – Small Anim Pract, 21*(6), 1241–1264.

Frazier, D. L., Jones, M. P., & Orosz, S. E. (1995). Pharmacokinetic considerations of the renal system in birds: Part I. Anatomic and physiologic principles of allometric scaling. *J Avian Med Surg, 9*(2), 92–103.

Girling, S. (2004). Diseases of the digestive tract of psittacine birds. *In Practice, 26*(3), 146–153.

Gleeson, M. D., Guzman, D. S. M., Knych, H. K., Kass, P. H., Drazenovich, T. L., & Hawkins, M. G. (2018). Pharmacokinetics of a concentrated buprenorphine formulation in red-tailed hawks (*Buteo jamaicensis*). *Am J Vet Res, 79*(1), 13–20.

Guzman, D. S. M., Zhu, Z., Summa, N., & Paul-Murphy, J. R. (2017). Pharmacokinetics of a sustained-release formulation of meloxicam after subcutaneous administration to Hispaniolan Amazon parrots (*Amazona ventralis*). *Journal of Avian Medicine and Surgery, 31*(3), 219–224.

Hawkins, M. G., Guzman, S.-M., Beaufrere, H., Lennox, A. M., & Carpenter, J. W. (2017). Birds. In J. W. Carpenter & C. J. Marion (Eds.), *Exotic animal formulary* (pp. 167–375). Elsevier Health Sciences.

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. *J Vet Pharmacol., 31*(3), 220–229.

Hunter, R. P. (2010). Interspecies allometric scaling. In F. Cunningham, J. Elliott, & P. Lees (Eds.), *Handbook of experimental pharmacology, vol 199 – comparative and veterinary pharmacology* (pp. 139–157). Springer-Verlag.

Kinobe, R. T., & Miyake, Y. (2020). Evaluating the anti-inflammatory and analgesic properties of maropitant: A systematic review and meta-analysis. *Meta-Analysis, 259–260*, 105471.

Kraus, B. L. H. (2013). Efficacy of maropitant in preventing vomiting in dogs premedicated with hydromorphone. *Veterinary Anaesthesia and Analgesia, 40*(1), 28–34.

Martin-Flores, M., Sakai, D. M., Learn, M. M., Mastrocco, A., Campoy, L., Boesch, J. M., & Gleed, R. D. (2016). Effects of maropitant in cats receiving dexmedetomidine and morphine. *J Am Vet Med., 248*(11), 1257–1261.

Narishetty, S. T., Galvan, B., Coscarelli, E., Aleo, M., Fleck, T., Humphrey, W., & McCall, R. B. (2009). Effect of refrigeration of the antiemetic Cerenia (maropitant) on pain on injection. *J Vet Pharmacol Ther, 10*(3), 93.

Nascimento, S. T., Silva, I. J. O. D., Mourão, G. B., & Castro, A. C. D. (2012). Bands of respiratory rate and cloacal temperature for different broiler chicken strains. *Rev Bras de Zootec, 41*(5), 1318–1324.

Niyom, S., Boscan, P., Twedt, D. C., Monnet, E., & Eickhoff, J. C. (2013). Effect of maropitant, a neurokinin-1 receptor antagonist, on the minimum alveolar concentration of sevoflurane during stimulation of the ovarian ligament in cats. *Vet Anaesth Analg, 40*(4), 425–431.

O'Connor, T. M., O'Connell, J., O'Brien, D. I., Goode, T., Bredin, C. P., & Shanahan, F. (2004). The role of substance P in inflammatory disease. *J Cell Physiol, 201*, 167–180.

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.

Ramsey, D. S., Kincaid, K., Watkins, J. A., Boucher, J. F., Conder, G. A., Eagleson, J. S., & Clemence, R. G. (2008). Safety and efficacy of injectable and oral maropitant, a selective neurokinin1 receptor antagonist, in a randomized clinical trial for treatment of vomiting in dogs. *J Vet Pharmacol Ther, 31*(6), 538–543.

Rau, S. E., Barber, L. G., & Burgess, K. E. (2010). Efficacy of maropitant in the prevention of delayed vomiting associated with administration of doxorubicin to dogs. *Journal of Veterinary Internal Medicine, 24*(6), 1452–1457.

Sadar, M. J., McGee, W. K., Au, G. G., Kendall, L. V., Gustafson, D. L., & Boscan, P. (2022). Pilot pharmacokinetics of a higher dose of subcutaneous maropitant administration in healthy domestic rabbits (*Oryctolagus cuniculus*). *J Exot Pet Med., 41*, 1–2.

Sedlacek, H. S., Ramsey, D. S., Boucher, J. F., Eagleson, J. S., Conder, G. A., & Clemence, R. G. (2008). Comparative efficacy of maropitant and selected drugs in preventing emesis induced by centrally or peripherally acting emetogens in dogs. *J Vet Pharmacol Ther, 31*(6), 533–537.

Smith, F. M., West, N. H., & Jones, D. R. (2000). The cardiovascular system. In G. C. Whittow (Ed.), *Sturkie's avian physiology* (5th ed., pp. 141–231). Academic Press.

Souza, M. J., Gerhardt, L. E., Shannon, L., Fortner, C., Davis, R., & Condon, C. S. K. (2021). Breed differences in the pharmacokinetics of orally administered meloxicam in domestic chickens (*Gallus domesticus*). *J Am Vet Med., 259*(1), 84–87.

Tanihata, S., Oda, S., Kakuta, S., & Uchiyama, T. (2003). Antiemetic effect of a tachykinin NK1 receptor antagonist GR205171 on cisplatin-induced early and delayed emesis in the pigeon. *Eur J, 461*(2–3), 197–206.

Trepanier, L. A. (2015). *Maropitant: Novel antiemetic* (pp. 75–77). Clinicians Brief University of Wisconsin-Madison.

Vail, D. M., Rodabaugh, H. S., Conder, G. A., Boucher, J. F., & Mathur, S. (2007). Efficacy of injectable maropitant (Cerenia™) in a randomized clinical trial for prevention and treatment of cisplatin-induced emesis in dogs presented as veterinary patients. *Vet Comp Oncol, 5*(1), 38–46.