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ORIGINAL ARTICLE

Multidose pharmacokinetics and safety of a modified, compounded theophylline product in dogs

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Abstract

Theophylline is used in canine medicine for the management of chronic bronchitis and bradyarrhythmias, yet no species-validated commercial products are available. This study reports the single-dose and multidose pharmacokinetics and safety of a modified, compounded theophylline (MCT) product readily available from a well-established, USP-compliant compounding pharmacy, which may be a suitable and reliable source for theophylline for dogs. Eleven dogs underwent serial plasma theophylline measurement following 10 mg/kg MCT PO. After a 7 days washout, dogs received 10 mg/kg MCT PO q12h and serial plasma theophylline quantification was repeated after the ninth dose. Dogs were monitored for potential adverse effects. For the nine dogs that completed the study, plasma theophylline concentrations were between 5 and 30 μg/ml for 91 +/− 15% of the dosing interval. There was no significant difference in half-life between single-dose and multidose administration. The most common adverse effects reported were mild and included agitation, excitement, and increased activity. The results of this study support the use of 10 mg/kg MCT administered twice daily as a starting dosage in dogs. This regimen appears safe, achieves appropriate plasma drug concentrations in most dogs, and does not cause significant changes in pharmacokinetic properties at steady state. Because compounded drugs do not undergo consistent testing for identity, quality, strength, purity, and stability, results of research described in reports using compounded products may not be reproducible.

KEYWORDS
airway, bradyarrhythmia, bronchodilator, chronic bronchitis

1 | INTRODUCTION

Theophylline is an important drug used for treatment of chronic canine bronchitis and bradyarrhythmias via its presumed bronchodilatory and positive chronotropic effects, respectively (Fox et al., 1999; Hawkins & Papich, 2014). There are currently no theophylline formulations approved for the use in dogs. Several human theophylline products have demonstrated high bioavailability and pharmacokinetics appropriate for twice-daily dosing in dogs (Bach et al. 2004; McKiernan et al. 1981; Mengozzi et al., 1998; Koritz et al., 1986). However, none of these are currently available in North America, which may reflect the decline of theophylline use in human medicine (Hawkins & Papich, 2014). An oral, modified, and compounded theophylline product (MCT), which could fulfill this need, is available through a veterinary, compounding pharmacy (Wedgewood Pharmacy) and meets United States Pharmacopeia standards for solid dosage forms (Cavett et al., 2019; United States Pharmacopoeia, 2014). The MCT combines theophylline with methylcellulose intended to slow dissolution and absorption (Sanghavi et al., 1990). Recently, we established single-dose pharmacokinetics of 10 mg/kg PO MCT and found that it was overall well absorbed

(bioavailability 96.2 ± 32.9%) and had a relatively long half-life (8.85 ± 3.63 h), potentially making it appropriate for twice-daily dosing (Cavett et al., 2019). However, based on calculated accumulation ratios (AR, 1.41–1.93), significant drug accumulation was expected, making concentrations at steady-state concentrations difficult to predict (Scheerans et al., 2015). To our knowledge, only one other study has investigated drug concentrations after multidose administration of any theophylline product in dogs (Mengozzi et al., 1998). However, only the maximum concentration and concentration at the end of the dosing interval were reported; full pharmacokinetic analysis was not performed. Therefore, it is unknown whether drug accumulation saturates elimination processes. This could cause clinically relevant changes in the theophylline terminal rate constant (λ_z) and half-life ($t_{1/2}$) leading to discrepancies between predicted and experimental steady-state concentrations.

Adverse effects during repeated theophylline administration have also not been fully explored. In single-dose experiments, orally administered theophylline did not elicit adverse cardiac or neurologic effects in dogs at plasma concentrations below 37 μg/ml (Munsiff, McKiernan, Neff-Davis, Koritz, 1988). In our previous investigation, the highest predicted individual plasma concentration at steady state was 26 μg/ml when administering the MCT orally at 10 mg/kg q12h, suggesting this dosage regimen would not cause adverse effects (Cavett et al., 2019). However, steady-state predictions are less accurate when more accumulation is expected (Scheerans et al., 2015). In their multidose study, Mengozzi et al., (1998) did not observe any signs of toxicity including vomiting, tremors, seizures, or arrhythmias over 9 days of twice-daily theophylline administration. All dogs included were young, male Beagles housed in a laboratory setting. Thus, it is possible that dogs of different ages, breeds, or environment could respond differently or that adverse effects other than those monitored above could occur.

Given the poorly defined disposition and adverse effects of theophylline at steady state, a multidose pharmacokinetic study is needed to make rational dosing recommendations for the MCT. Therefore, the primary objective of this study was to establish the pharmacokinetic properties of the MCT at steady state in dogs. Of particular interest was whether twice daily, oral administration at 10 mg/kg can sustain plasma theophylline concentrations within a therapeutic range of 5–30 μg/ml throughout the dosing interval. This range was selected based on previous studies documenting increased ventilatory drive and tidal volumes above 5 μg/ml and lack of adverse effects below 37 μg/ml in dogs (Aubier, Murciano, Viires, Lecocguic, Palacios, & Pariente, R, 1983; Munsiff et al., 1988). A secondary objective was to determine the adverse effects of the MCT following multiple doses.

2 | MATERIALS AND METHODS

2.1 | Animals

Eleven healthy adult dogs were recruited from the pet population of the students, faculty, and staff of the University of Illinois, Veterinary Teaching Hospital. Dogs were deemed healthy based on a physical examination performed by a board-certified small animal internist (JR), complete blood count, biochemistry profile, urinalysis, systolic blood pressure (SBP) measured by the Doppler method (Acierno et al., 2018), and 5 min, 6-lead electrocardiogram (ECG) using the CardioScout VET-ECG System (Dextronix Inc.) reviewed by a board-certified veterinary cardiologist (SK). Dogs receiving medications other than routine flea, tick, and heartworm prophylaxis were excluded. This study was approved by the University of Illinois Institutional Animal Care and Use Committee (protocol #19029).

2.2 | Modified Compounded Theophylline (MCT) Product

Following study admission, a 10 mg/kg MCT dose rounded to the nearest 10 mg place was compounded in separate batches for each dog by Wedgewood Pharmacy. The MCT is available in a gelatin capsule with methylcellulose and microcrystalline cellulose as excipients. Product concentration and stability of the MCT have previously been documented (Cavett et al., 2019).

2.3 | Experimental Design

This study was performed in two phases: a single-dose phase and a multidose phase, separated by at least a 7 days washout period based on a previously established MCT terminal half-life of 8.67 h (range 6.75–11.38 h) (Cavett et al., 2019). For the single-dose phase, dogs were admitted to the Veterinary Teaching Hospital and orally administered the MCT with their normal morning meal. Sample collection and cardiovascular parameter measurement were performed serially before and 2, 4, 6, 8, 10, 12, 18, 24, and 48 h after drug administration. At each time point, SBP measurement and a 2 min 6-lead ECG were performed in right lateral recumbency. Following these measurements, 5 ml of EDTA whole blood was collected for plasma theophylline concentration measurement via jugular, cephalic, or saphenous venipuncture.

Following the washout period, the owners were instructed to begin administering 10 mg/kg MCT q12h orally at home for 4 days (8 doses). This duration was selected based on the previously established MCT terminal half-life (Cavett et al., 2019), assuming five half-lives to achieve steady state, and including additional time to account for individual variation in half-life not captured in our original study. During at-home MCT administration, owners were instructed to observe for potential adverse effects using a standardized form (Supporting Informationf) at least twice daily. Monitoring parameters included mentation, agitation level, excitement level, vomiting, diarrhea, changes in urination, appetite, and activity level. Heart rate was also determined twice daily by owners, all of whom were practicing veterinarians, veterinary technicians, or veterinary students with at least 1 year of formal training. On the fifth day of the multidose phase, dogs were admitted to the Veterinary Teaching Hospital and administered the ninth and final

MCT dose with their normal food ration. Blood sample collection, SBP measurement, and ECG were performed as described for the single-dose phase.

2.4 | Plasma Theophylline Concentration Analysis

Following collection, EDTA whole blood samples were stored at 4°C for a maximum of 4 h prior to processing. Plasma was separated by centrifugation at 1,800 × g for 10 min and stored at − 80°C until analysis. Plasma theophylline concentrations were quantified as previously described (Cavett et al., 2019).

2.5 | SBP Measurement and ECG Analysis

At each time point, SBP was measured by the Doppler method (Acierno et al., 2018). Five readings were collected sequentially, the highest and lowest readings were discarded, and the remaining three were averaged to obtain a single, final SBP measurement for each dog at each time point. ECG tracings were examined using the VET-ECG Software (Dextronix Inc.). An average heart rate for each dog, for each time point, was calculated by averaging the heart rate of two randomly selected 6 sec segments within the 2 min tracing. Each recording was also examined for arrhythmias by a board-certified veterinary cardiology (RF, SK).

2.6 | Statistical Analysis

Quantitative data are presented as mean + / − standard deviation. For both the single-dose and multidose phases, non-compartmental pharmacokinetic analysis was performed using Phoenix WinNonLin 8.1.0 (Certara Inc). An AR was also calculated:

$$AR = \frac{AUC_{MD}}{AUC_{SD}}$$

where AUC_{SD} and AUC_{MD} are the area under the curve from zero to infinity ($AUC_{0-\infty}$) of the single-dose and multidose phases, respectively. To evaluate for relevant changes in drug disposition at steady state, the time to maximum concentration (T_{MAX}) and $t_{1/2}$ were compared between the single-dose and multidose phases using a paired t test. The ability of the MCT (10 mg/kg PO q12h) to sustain therapeutic plasma theophylline concentrations at steady state was assessed by determining the percentage of time each dog's drug concentrations remained between 5 and 30 μg/ml during the first 12 h of the multidose sampling period, equivalent to a single dosing interval.

The incidence of adverse effects reported by owners during at-home drug administration is reported as the total number of times an adverse effect occurred and the total number of dogs experiencing at least one instance over the 4 days period. The incidence of clinically relevant changes in heart rate, SBP, and ECG morphology during both the single-dose and multidose sampling phases is also reported. To assess the potential impact of the MCT on heart rate and SBP, correlation between each of these parameters and plasma theophylline concentration was determined using the Pearson's correlation coefficient. All statistical testing was performed using commercial software (Prism 8, GraphPad Software Inc.). Significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Study Population

Eleven healthy dogs were recruited with a mean age of 4.5 + / − 2.0 years (range 1–7 years) and mean weight of 27.1 + / − 8.1 kg (range 15.1–44.0 kg). The population included six male castrated, four female spayed, and one male intact dogs. Breeds included five mixed-breed dogs, two poodles, and one of each of the following: Australian cattle dog, Labrador retriever, Boxer. All 11 dogs completed the single-dose phase; nine dogs completed the multidose phase; two were withdrawn from the study by their owners during the at-home administration period for possible adverse effects.

3.2 | Single and Multidose Pharmacokinetics

Pharmacokinetic parameters from non-compartmental analysis of the single-dose and multidose phases are presented in Table 1 and Figure 1. The mean AR was 1.63 + / − 0.50 (range 0.93–2.60). There was no significant difference in T_{MAX} ($p = 0.471$) or $t_{1/2}$ ($p = 0.205$) between the single-dose and multidose phases (Figure 2). Data and analyses for individual animals are provided in Supporting Information.

For the multidose phase, the average time plasma theophylline concentrations were within the proposed therapeutic range (5–30 μg/ml) during the dosing interval was 91 + / − 15%. Of the nine dogs that completed the multidose phase, six dogs had plasma concentrations within the therapeutic range for 100%, one dog for 83%, and two dogs for 67% of the dosing interval.

3.3 | Adverse Effects

Data from the at-home monitoring forms were available for 10/11 dogs. Eight instances of agitation (five mild, two moderate, and one severe) were reported in four dogs. Twelve instances of increased excitement were reported in four dogs, and one instance of decreased excitement was reported in one dog. Three dogs experienced vomiting, one episode each, and one dog experienced a single episode of diarrhea. Six instances of polyuria were reported in two dogs. Two instances of inappetence were reported in one dog. Eight instances of increased activity were reported in two dogs, and three instances of

TABLE 1 Non-compartmental analysis of single and multidose administration of 10 mg/kg MCT by mouth. AUC = area under the curve; AUC_{0-t} = observed area under the curve; $AUC_{0-\infty}$ = area under the curve extrapolated to infinity; $AUC_{0-\infty}$/dosage = area under the curve extrapolated to infinity normalized to dosage; $AUMC_{0-\infty}$ = area under the moment curve extrapolated to infinity; $AUMC_{0-t}$ = observed area under the moment curve; $AUC_{\%EXTRAP}$ = percent of the $AUC_{0-\infty}$ extrapolated to infinity; $AUMC_{\%EXTRAP}$ = percent of the $AUMC_{0-\infty}$ extrapolated to infinity; C_{MAX} = maximum plasma concentration; λ_z = terminal rate constant; MCT = modified compounded theophylline; MRT = mean residence time; $t_{1/2}$ = terminal half-life; T_{MAX} = time to C_{MAX}

	Single-Dose Phase				Multidose Dose			
Parameter	Mean	SD	Min	Max	Mean	SD	Min	Max
Dosage (mg/kg)	10.41	0.87	9.01	12.30	10.21	0.97	8.86	12.25
λ_z (h^{-1})	0.08	0.02	0.04	0.11	0.10	0.04	0.05	0.17
$t_{1/2}$ (h)	9.04	2.69	6.05	16.05	8.20	3.02	3.97	13.71
T_{MAX} (h)	4.73	2.05	2.00	8.00	4.22	1.20	2.00	6.00
C_{MAX} (μg/ml)	11.06	2.12	7.48	14.50	16.43	5.49	11.50	27.60
AUC_{0-t} (h*μg/ml)	147.14	35.26	83.88	201.97	249.56	124.06	123.42	475.40
$AUC_{0-\infty}$ (h*μg/ml)	159.41	48.55	84.33	256.29	259.66	137.71	124.72	524.27
$AUC_{0-\infty}$/dosage (μg*h/ml/mg/kg)	15.22	4.18	8.71	24.31	25.14	12.53	12.75	48.14
$AUC_{\%EXTRAP}$ (%)	5.62	10.88	0.53	38.21	2.68	3.10	0.05	9.32
$AUMC_{0-t}$ (h^2*μg/ml)	1912.51	626.23	719.44	3002.43	3159.82	2161.92	1295.43	7571.55
$AUMC_{0-\infty}$ (h^2*μg/ml)	2537.68	1445.21	744.95	6301.21	3819.51	3189.40	1356.96	10883.82
$AUMC_{\%EXTRAP}$ (%)	15.39	19.68	3.04	73.28	10.33	10.26	0.30	30.43
MRT (h)	15.08	4.08	8.83	24.59	13.22	3.93	8.56	20.76

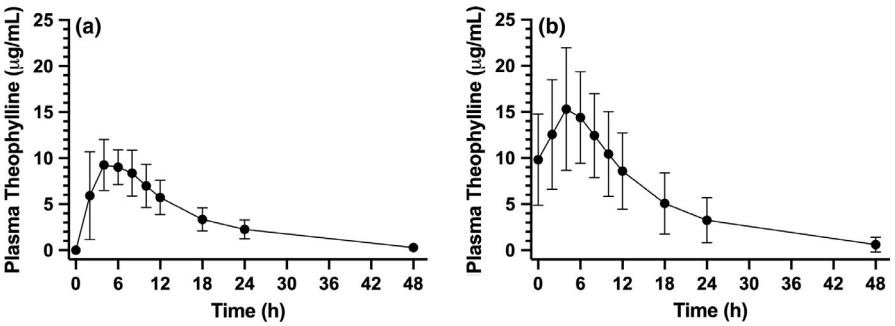

FIGURE 1 Concentration-time curves of 10 mg/kg PO MCT (a) after a single-dose and (b) after the final dose in the multidose protocol, at steady state. MCT = modified, compounded theophylline

decreased activity were reported in two dogs. No bradycardia, tachycardia, or changes in mentation were recorded in any dog throughout the at-home drug administration period. Two dogs were withdrawn from the study by their owners during this period, one for severe agitation on day two and one for an episode of vomition on day four.

During both the single-dose and multidose phases, no clinically relevant changes in heart rate or blood pressure occurred. One dog had a single ventricular premature complex 12 h post-drug administration in the single-dose phase (theophylline concentration = 5.32 μg/ml). Two dogs each had a single instance of type I, second-degree atrioventricular block, one 2 h post-administration (0.628 μg/ml), and one 24 h post-administration (2.49 μg/ml), both in the single-dose phase. All other ECG tracings revealed a normal sinus rhythm or sinus arrhythmia. Based on the r-value, there was a weak, positive correlation between plasma theophylline concentrations and heart rate ($r = 0.339$, $p < 0.001$, Figure 3a). However, there was no significant correlation between theophylline concentrations and SBP ($r = -0.114$, $p = 0.155$, Figure 3b).

4 | DISCUSSION

Theophylline has been a standard drug in the management of canine chronic bronchitis, yet no commercial products that have previously been validated in dogs are currently available. One potential solution to this dearth of validated formulations is to use theophylline products from a reputable, well-established compounding pharmacy. We recently established the single-dose pharmacokinetics of one such product, the MCT. Despite not possessing extended-release properties, twice-daily administration of 10 mg/kg MCT was predicted to yield therapeutic plasma concentrations in most dogs (Cavett et al., 2019). However, a relatively large amount of drug accumulation was expected making steady-state concentrations more difficult to predict. Thus, we pursued a multidose pharmacokinetics study of the MCT to evaluate theophylline concentrations at steady state. Overall, our results support twice-daily administration of 10 mg/kg MCT as a starting dosage for use in dogs. This regimen yielded theophylline

concentrations above 5 μg/ml throughout the dosing interval in the majority of the study population and appears to be safe.

After a single 10 mg/kg dose of the MCT, pharmacokinetic parameters were very similar to what we have previously reported for this product (Cavett et al., 2019) demonstrating consistency in the product as well as between the two studies. Just as before, interindividual differences were present, likely influenced by variation in bioavailability and elimination. Our single-dose results also mirror those of another study investigating two commercial products in a heterogenous dog population, which reported half-lives of 8.4 + / − 1.2 and 10.9 + / − 3.6 h (Mengozzi et al., 1998). In this multidose phase, the majority of dogs (6/9) maintained plasma theophylline concentrations within a range of 5–30 μg/ml for the entire 12 h dosing interval. The other three dogs had concentrations within the range for at least 8 h but then dropped below 5 μg/ml for 2–4 h during that interval, which may be subtherapeutic. No dog had plasma concentrations above 30 μg/ml at any time indicating significant theophylline toxicity may be unlikely when dosed at 10 mg/kg MCT orally, q12h. These findings suggest that this regimen may be appropriate to recommend for dogs beginning therapy with the MCT. However, because interindividual variation does exist, some dogs may require dose adjustments, ideally based on therapeutic drug monitoring.

In the present study, we used a therapeutic range of 5–30 μg/ml. Unfortunately, the true therapeutic range for theophylline in dogs remains unknown due to a lack of pharmacodynamic studies for theophylline's bronchodilatory properties and lack of efficacy trials in clinical patients. Most previously published canine studies have used a therapeutic range of 10–20 μg/ml (Bach, et al., 2004; McKiernan, Neff-Davis, Koritz, Davis, & Pheris, 1981; Koritz et al., 1986), which has been shown to have bronchodilatory effects in adult humans (Weinberger, 1984). However, at least one study in dogs used a lower range limit of 5 μg/ml (Mengozzi, et al., 1988). This may be appropriate because other positive effects of theophylline have been documented in both dogs and humans at plasma concentrations below 10 μg/ml including immunomodulation, increased respiratory drive, and increased tidal volume (Aubier et al., 1983; Page, 1999). The upper end of the therapeutic range is typically set at 20 μg/ml because concentrations above this cause common and predictable adverse effects in humans including profound nausea and irritability, with the possibility of arrhythmias, tremors, and seizures (Barnes, 2010). However, dogs are more resistant to the adverse effects of theophylline. In one toxicity study, dogs did not show adverse effects until plasma concentrations reached 37–60 μg/ml (Hamlin & Sally, 1993; Munsiff et al., 1988). Even then, the adverse effects observed were relatively mild, including sinus tachycardia and central nervous stimulation. Furthermore, plasma concentrations up to 90 μg/ml did not appear to induce significant arrhythmias in awake canine patients (Hamlin & Sally, 1993; Munsiff et al., 1988). Taken together, these data suggest that the wider therapeutic target range of 5–30 μg/ml for theophylline may be more appropriate in dogs.

One reason we elected to perform a multidose study for the MCT, rather than relying on single-dose data, is that a significant amount of drug accumulation is expected for the MCT when dosed twice daily (Cavett et al., 2019). Thus, steady-state predictions for this product may be less reliable compared with drugs with faster elimination and less accumulation. Our results demonstrate that significant drug accumulation does occur with the MCT at steady state as evidenced by a high AR (1.63 + /− 0.50). The only other study to evaluate theophylline at steady state in dogs (Mengozzi et al., 1998) also demonstrated significant drug accumulation for two commercial extended-release products with a 28–48% increase in C_{MAX} compared with single-dose pharmacokinetics.

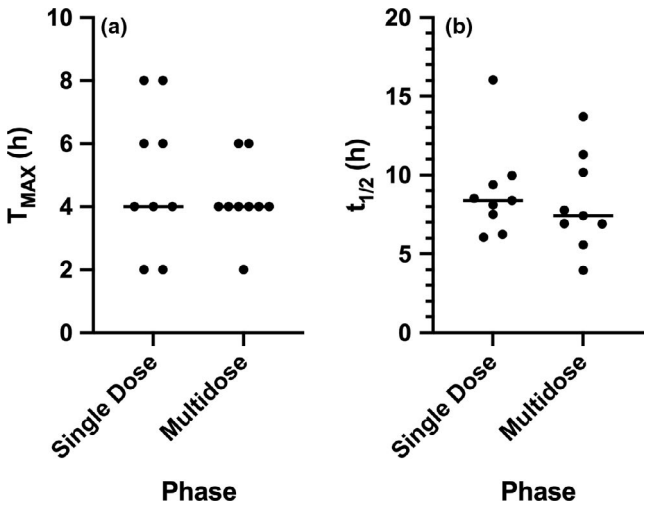

FIGURE 2 Comparison of (a) T_{MAX} and (b) $t_{1/2}$ between single-dose and multidose phases. There was no significant difference between the two phases for either T_{MAX} (p = 0.471) or $t_{1/2}$ (p = 0.205). T_{MAX} = time to maximum concentration; $t_{1/2}$ = half-life

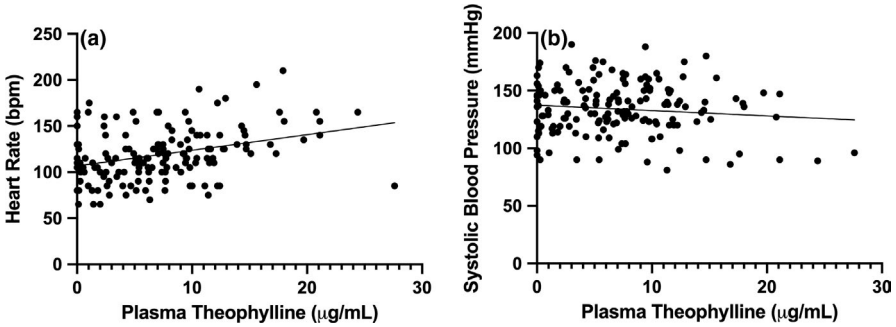

FIGURE 3 Correlation between plasma theophylline concentrations and (a) heart rate and (b) SBP. There was a weak, positive correlation between plasma theophylline concentrations and heart rate (r = 0.339, p < 0.001) but no significant correlation between theophylline concentrations and SBP (r = − 0.114, p = 0.155). SBP = systolic blood pressure

Therefore, the MCT has accumulation properties akin to previously validated commercial theophylline formulations. However, the MCT did show significant interindividual variation in the AR (range 0.93–2.60). These differences are most likely due to variation in elimination between dogs, which is primarily mediated by hepatic cytochrome P450 metabolism. Many of these enzymes are highly polymorphic, so individual genetic variants may impact theophylline pharmacokinetics (Court, 2013). Furthermore, breed-based differences in theophylline pharmacokinetics have been documented suggesting heritability (Kukanich & Nauss, 2012). Thus, genetics likely account for at least some of the interindividual variation seen with the MCT and should be considered as a potential cause if lack of efficacy is observed.

Another factor that can influence hepatic elimination at steady state in is induction or saturation of drug-metabolizing enzymes, which would decrease or increase clearance, respectively. To our knowledge, changes in elimination at steady state have not been investigated for any theophylline product in dogs as the only other canine multidose theophylline study did not report full pharmacokinetic analysis for their multidose data (Mengozzi et al., 1988). In the present study, we found no significant differences in $t_{1/2}$, which is inversely proportional to λ_z, after a single dose of the MCT vs. at steady state. In our previous study, we found no evidence of flip-flop kinetics (Cavett et al., 2019), so λ_z should be primarily driven by elimination, not absorption. As there is no difference in $t_{1/2}$ (or λ_z) between phases, we can conclude that there are no significant changes in elimination after multiple doses of the MCT. Thus, the accumulation identified by this study is simply due to slow elimination and relatively frequent administration, rather enzyme induction or saturation. There were also no significant changes in T_{MAX} between the single-dose and multidose phases, suggesting that there are no major changes to the absorption profile the MCT after multiple doses.

In addition to pharmacokinetics, we also investigated adverse effects of the MCT, both during at-home drug administration and while in hospital. A number of adverse effects were reported by owners while administering the MCT at home, but most were mild and were unlikely to preclude use. The most common changes seen at home were behavior related including agitation, excitation, and changes in activity level. However, because no control group was used and owner observations were subjective, it is difficult to know whether these changes were truly related to the drug or represented normal behavioral variation. Interestingly, two animals were reported to have polyuria, which, to our knowledge, is not a previously reported adverse effect of theophylline in dogs. However, methylxanthines do have diuretic action via adenosine inhibition in mouse models and polyuria is a known adverse effect of theophylline in humans so similar mechanisms may be present in the dog (Bell et al., 1998; Rieg et al., 2005). In contrast to our study, Mengozzi et al., (1998) did not observe any adverse effects during multidose administration of theophylline. A difference in observers (owner vs. investigator) may partially explain the difference in adverse effect profiles. Furthermore, Mengozzi et al. used young, male, laboratory Beagles, whereas our study recruited from the pet dog population, so it is possible that age, breed, or housing conditions could impact the incidence of adverse effects.

While in hospital, some dogs did experience mild tachycardia and mild systemic hypertension; these were thought to be related to stress and adjusting to the hospital environment given that changes were most prominent during the admit visit and the beginning of the single-dose phase, prior to any drug administration. This is corroborated by the fact that no episodes of tachycardia were reported by owners, all of whom were veterinary professionals, during at-home drug administration. Interestingly, there was a mild, positive correlation between heart rate and plasma theophylline concentration. A similar relationship has been previously described, but at much higher doses (160 mg/kg) and resulting plasma concentrations (Munsiff et al., 1988). Thus, it appears that the MCT does not cause significant tachycardia at the plasma concentrations investigated in this study, but it is possible that theophylline could be useful in increasing sinus node depolarization. This hypothesis requires testing in clinically affected patients and the therapeutic range for this indication may be different from that for chronic bronchitis. Arrhythmias also appear unlikely at the theophylline concentrations resulting from 10 mg/kg q12h MCT. The two instances of type I second-degree atrioventricular block are physiologic arrhythmias, the result of high vagal tone and unrelated to MCT administration. One dog had one ventricular premature contraction throughout the entire study, which theoretically could be caused by theophylline. However, the plasma drug concentration was low when this occurred (5.32 μg/ml), so this single ventricular arrhythmia is most likely due to normal variation given that other studies examining much higher plasma concentrations have failed to identify ventricular arrhythmogenicity of theophylline in dogs (Hamlin & Sally, 1993; Munsiff et al., 1988).

Our study has several limitations that should be addressed. First, the MCT is a compounded product, which could introduce variability between batches. Because compounded drugs do not undergo consistent testing for identity, quality, strength, purity, and stability, results of research described in reports using compounded products may not be reproducible. However, we have previously demonstrated the potency and stability of this product (Cavett et al., 2019). Furthermore, Wedgewood Pharmacy maintains high standards in accordance with United States Pharmacopeia chapters 795 and 797 and has been in business for over 40 years. Thus, the MCT may be a more reliably available source for theophylline than commercial formulations, of which there are none currently validated for dogs. Our sample size was also relatively small, so our data may not capture the full range of interindividual variation seen within the canine population. A population pharmacokinetics study would be of great interest to establish the effects of disease status, phenotypic characteristics, and genotype on theophylline disposition. Sample size was further reduced by the removal of two dogs during at-home drug administration due to perceived adverse effects by their owners. Unfortunately, the relationship between these events and

plasma theophylline concentrations could not be evaluated using the current study design. Finally, the lack of a species-specific therapeutic range for theophylline in dogs confounds our ability to make definitive dosage recommendations for the MCT. This highlights the importance of clinical monitoring in addition to therapeutic drug monitoring when evaluating a theophylline dosage regimen in an individual animal. The results of this study may support 10 mg/kg q12h orally as a safe starting dose for the MCT in dogs. Further dose adjustments should be based on a combination of clinical and therapeutic drug monitoring. Thus, the MCT appears to be a practical alternative to commercial theophylline products for canine use. Future investigations of the MCT and theophylline administration in general should focus on defining an evidenced-based therapeutic range in dogs through pharmacodynamic studies of theophylline's bronchodilatory properties and clinical trials of dogs with chronic bronchitis.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

JR contributed to the study design and execution, data analysis, and manuscript preparation. VC, CL, and CP contributed to the study design and execution and manuscript preparation. RF and SK contributed to the study design, data analysis, and manuscript preparation. ZL performed the sample analysis and contributed to the manuscript preparation. BM contributed to the study design and manuscript preparation.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the Supporting Information of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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