

STANDARD ARTICLE

The frequency of oral famotidine administration influences its effect on gastric pH in cats over time

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Background: Famotidine is commonly administered to cats. Prolonged famotidine administration results in decreased efficacy in humans, dogs, and cows, but the long-term effects in cats are unknown.

Objectives: To compare the effect of 2 oral administration frequencies of famotidine, twice daily (Group 1) and twice daily every second day (Group 2), on intragastric pH and serum gastrin concentrations in cats. We hypothesized a diminished effect on intragastric pH would be observed over time in Group 1 but not Group 2.

Animals: Sixteen healthy cats.

Methods: Randomized, 2-factor repeated measures crossover design. Cats received 0.5-1.24 mg/kg (median, 0.87 mg/kg) famotidine twice daily or twice daily every second day for 14 consecutive days. Intragastric pH monitoring was used to record intragastric pH on treatment days 1-3 and 11-13. Mean pH and mean percentage time (MPT) intragastric pH was ≥ 3 and 4 were compared between and within treatment groups by analysis of variance.

Results: Significant treatment group by time interactions were observed for mean intragastric pH, MPT intragastric pH ≥ 3 and 4 ($P = .009$, $P = .02$, $P = .005$, respectively). Interaction post hoc tests identified significant decreases in mean intragastric pH ($P = .001$), MPT ≥ 3 ($P = .001$), and MPT ≥ 4 ($P = .001$) on day 13 compared to day 1 in Group 1 but not in Group 2.

Conclusions and Clinical Importance: Oral famotidine administration results in a diminished effect on intragastric pH in healthy cats when given twice daily every day.

KEYWORDS

acid suppressant, feline, gastrin, H2RA, tolerance

1 | INTRODUCTION

Proton pump inhibitors (PPIs, eg, omeprazole) have superior acid suppressing efficacy compared to histamine-2 receptor antagonists (H2RAs, eg, famotidine) and are considered to be the treatment of choice for gastrointestinal (GI) ulceration in dogs and cats.¹⁻³ However, the aggressive acid suppression provided by PPIs may not always be desired. Famotidine continues to be widely used in veterinary medicine because it can provide immediate clinical relief and can

be administered with a full meal, unlike omeprazole which takes days to reach peak onset of action and must be administered on an empty stomach.⁴ Veterinarians also perceive that famotidine alleviates stomach upset in animals with chronic diseases, such as chronic kidney disease (CKD) and chronic enteropathies. For example, in 2 large retrospective studies of cats with CKD, famotidine was 1 of the top medications prescribed.^{5,6} The efficacy of prolonged famotidine administration can decrease over time in humans, dogs, and cows.^{4,7,8} In dogs, daily oral famotidine administration resulted in good acid suppression on days 1 and 2 but was no better than placebo at increasing intragastric pH by day 12.⁷ In a study of human subjects, a diminished acid suppressant effect appeared to be dependent on daily H2RA

Abbreviations: ANOVA, analysis of variance; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; MPT, mean percentage time; PPI, proton pump inhibitor; RAH, rebound acid hypersecretion.

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administration, whereas twice daily every second day administration did not result in tolerance.⁹

To our knowledge, the effects of oral famotidine administration on intragastric pH in cats over time have not been reported. Because famotidine is a commonly administered treatment in cats, determination if daily famotidine administration results in diminished acid suppression in cats is of interest. Our study objectives were to determine if twice daily oral famotidine administration led to tolerance and if the development of this effect required daily drug administration in cats. We hypothesized that daily oral famotidine administration would lead to a diminished effect on gastric pH over time.

2 | MATERIALS AND METHODS

2.1 | Study animals

The subjects of this study were 16 healthy adult cats from a research colony at the University of Tennessee (12 intact females, 1 spayed female, 2 castrated males, and 1 intact male), aged 3.2-4.2 years (median, 3.8 years), and weighing 3.0-6.4 kg (median, 4.6 kg). None of the cats showed clinical signs of GI disease, and they were deemed healthy based on history and available historical blood test results as well as normal physical examination, normal baseline blood test results (CBC, serum biochemistry profile, urinalysis) and negative fecal examinations using zinc and sugar sulfate centrifugation flotation methods performed within 6 months of study entry. The number of cats ($n = 16$) selected was based on a sample size calculation using a study evaluating the effect of intermittent administration of an H2RA blocker in people.¹⁰ By means of a high correlation (0.8) and power = 0.8, 14 cats were needed to identify a change of 13% in mean intragastric pH between treatment groups. An additional 2 cats were enrolled to account for the possibility of study dropout. Animals were cared for according to the principles outlined in the NIH Guide for the Care and Use of Laboratory Animals (approved IACUC protocol for this study #2312-0115).

2.2 | Study design

In a randomized, open label, 2-way crossover study design, all cats were treated using PO administered famotidine (Famotidine; Merck Consumer Pharmaceuticals Company, Deerfield, Illinois) at a dosage of 0.5-1.24 mg/kg (median, 0.87 mg/kg), twice daily ("Group 1") or twice daily every second day (twice daily q48h; "Group 2") for 14 consecutive days. The goal was to dose famotidine as close to 0.5-1 mg/kg q12h as possible. This dose was achieved by administering one-quarter to one-half tablet and was kept consistent across treatment arms. Cats were randomized to a treatment schedule by a random number generator, so that 8 cats were randomized to each group. Cats were fed and medicated at approximately 6:30 AM and 6:30 PM. The feeding schedule and dosage interval were maintained throughout the study period. Cats received 1 cup of dry food (Purina One Tender Selects Blend with Real Salmon Adult Dry Cat Food; Nestle Purina PetCare Company, St. Louis, Missouri) twice daily and were allowed free access to the food throughout the day to mimic the feeding schedule of many client-owned cats. The amount

of dry food remaining from the previous meal was measured to monitor appetite, discarded, and replaced twice daily. At the same time, cats also received 1 tablespoon of canned food (Science Diet Kitten Savory Salmon Entrée Canned Cat Food; Hill's Pet Nutrition, Inc., Topeka, Kansas) twice daily, which contained famotidine on treatment days and did not contain famotidine on "off" days. Swallowing of the medication was witnessed, and if cats did not voluntarily eat the famotidine tablet, it was administered using a pill gun. Cats had unlimited access to water during the pH monitoring period. Clinical signs, including change in attitude, vomiting, and fecal character, were recorded twice daily. Feces were graded from 1 to 7 based on a standardized fecal scoring system, and diarrhea was defined as a fecal score of >4 (Fecal Scoring System; Nestle Purina PetCare Company). An episode of inappetence was defined as <50% of the meal ingested. Vomitus was evaluated for the presence of medication or pH capsule when it occurred. A period of 7 weeks separated treatment groups with no medications administered during this period.

2.3 | Intragastric pH monitoring

The Bravo pH monitoring system (Bravo pH capsule with delivery system; Given Imaging, Duluth, Georgia) was placed by radiographic guidance under sedation as previously described.¹¹ All pH capsules and receivers were calibrated as previously described according to the manufacturer's instructions.³ Location of each pH capsule was kept consistent in each cat between treatment groups by utilizing the measurements on the capsule delivery device to measure the distance from the maxillary canine teeth to the area of capsule placement in the fundus based on radiographs. One day before the first treatment period (day 0, baseline) and after an overnight fast, cats were sedated with 10 µg/kg dexmedetomidine (Dexdomitor 0.5 mg/mL injection; Orion Pharma, Espoo, Finland) IV and 0.4 mg/kg butorphanol (Torbugesic 10 mg/mL injection; Fort Dodge Animal Health, Fort Dodge, Iowa) IV. The cats were placed in right lateral recumbency. The pH capsule was then blindly introduced transorally into the proximal stomach as previously described.¹¹ Sedation was reversed with 10 µg/kg atipamezole (Antisedan 5 mg/mL injection; Orion Pharma, Espoo, Finland) IM after pH capsule placement. The pH capsule placement was repeated in the same manner on day 11 of the treatment period (Figure 1).

2.4 | pH recordings

Intragastric pH recordings were obtained telemetrically at 6-second sampling intervals. Twenty-four-hour intragastric pH recording was initiated immediately after placement and acquired continuously for as long as the capsule remained in the stomach, often up to 96 hours (24-hour baseline data and treatment days 1-3). The corresponding data receivers were kept on the side of each cat's cage during the data acquisition phase. The pH data were uploaded to the computer using a software package provided by the manufacturer (Polygram Net Software; Given Imaging, Yoqneam, Israel) every 48 hours for each monitoring period. After data upload, data from the receiver were cleared and the same receiver was used to obtain data for the next 48-hour period. New capsules were placed on day 11 and continuously

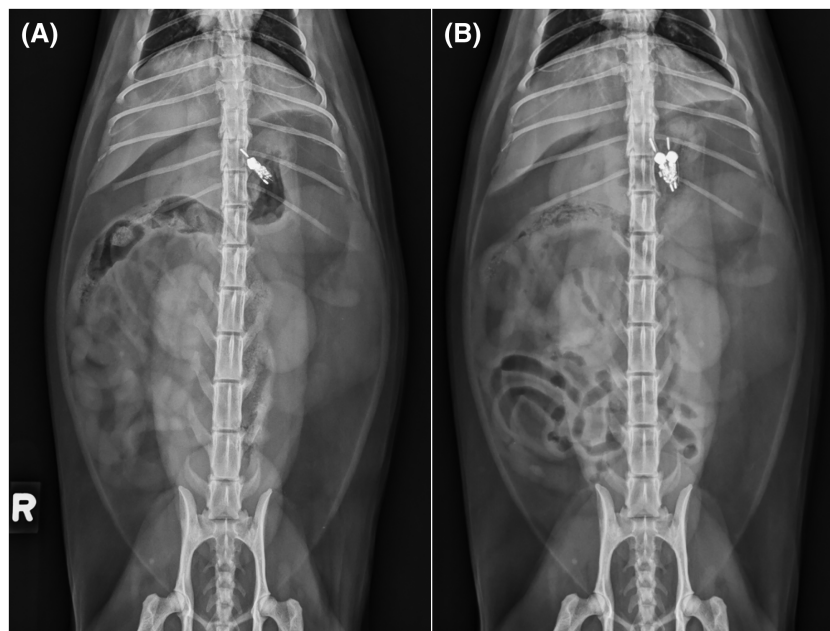


FIGURE 1 Ventrodorsal radiograph on day 0 (A) versus day 11 (B) confirming similar radiographic placement of the pH capsule using measurement system on capsule delivery device

monitored until day 15. Data were included from days 0 to 15 to include pretreatment and posttreatment days when possible (ie, whenever the pH capsule remained in the stomach of the cat). Passage of the capsule out of the stomach was defined by a rapid and persistent increase in pH >4 as previously described.¹²

2.5 | Serum gastrin concentrations

At baseline (day 0) and on treatment days 2 and 11, 3 mL of blood was obtained by venipuncture of the jugular or medial saphenous vein after an overnight fast and after receiving sedation on days 0 and 11 and after an overnight fast without sedation on day 2. Serum was collected from clotted blood using serum clot activator tubes after centrifugation at 250g and stored in cryovials at -80°C . After study completion, the serum was shipped on dry ice to the Gastrointestinal Laboratory at Texas A&M University for measurement of serum gastrin concentrations. Serum gastrin concentrations were measured using an automated chemiluminescent, enzyme-labeled immunometric assay (Immulite 2000; Siemens Healthcare Diagnostics, Malvern, Pennsylvania) as previously described.¹³

2.6 | Statistical analysis

Mean pH and mean percentage time (MPT) intragastric pH ≥ 3 and ≥ 4 were calculated using the manufacturer software (Polygram Net Software; Given Imaging, Yoqneam, Israel). Statistical analysis was performed using commercial software (SAS software, version 9.54, Cary, North Carolina 27 513, USA, Release TS1M5). A 2-factor repeated-measures mixed-effects crossover design and corresponding analysis of variance (ANOVA) were performed to evaluate mean intragastric pH and MPT that intragastric pH were ≥ 3 and 4 for treatment, time (day of treatment), and period differences. To be conservative, a value of 9.9 ng/L was assigned to all gastrin data below the assay's limit of

detection (<10 ng/L). Serum gastrin concentrations and MPT that intragastric pH was ≥ 4 were then log transformed and analyzed by repeated-measures mixed model ANOVA to evaluate for treatment, time, treatment by time interaction, and period differences. Two time points (1, 13) were observed for mean intragastric pH and MPT that intragastric pH were ≥ 3 and 4, and 3 time points were observed for serum gastrin concentrations (days 0, 2, and 11). An additional 2-time point analysis comparing baseline to day 15 in each treatment group was performed to test for rebound acid hypersecretion (RAH). Unstructured Kronecker product variance/covariance structures were incorporated into each model.¹⁴ In each analysis, a contrast was developed to see whether mean values for day 1 were different than mean values for day 13 for each pH measurement under each treatment. A Shapiro-Wilk test for normality and QQ normality plots were used to evaluate normality of ANOVA residuals. Levene's equality of variances test was used to evaluate equality of treatment variances. All statistical assumptions regarding normality and equality of variances were met after a log transformation was applied to serum gastrin concentration and MPT that intragastric pH was ≥ 4 . No transformation was required for mean pH and MPT that intragastric pH was ≥ 3 . Statistical significance was defined as $P \leq .05$.

3 | RESULTS

3.1 | Capsule placement and pH monitoring

Of 64 pH capsules, 63 were successfully attached to the gastric fundic mucosa. On 1 occasion, the capsule failed to deploy from the delivery device (day 0, Group 2). This was thought to be attributable to a malfunction of the delivery device itself. The capsule was readministered PO and stayed in the stomach for days 0 and 1, and, therefore, this data was included in the statistical analysis. On 2 occasions in Group

1 on day 11, the capsules failed to sync with their respective wireless monitor, and, therefore, new capsules were replaced in the gastric fundus without complications. With respect to adhered capsules, on 2 occasions (both on day 12, Group 1), the Bravo pH capsule detached and exited the stomach before the end of the monitoring period. Data from these 2 cats therefore were not included in the treatment comparisons on day 13.

3.2 | Intra-gastric pH recordings

Mean intra-gastric pH and MPT intra-gastric pH ≥ 3 and ≥ 4 in a 24-hour period on days 1 and 13 were used for statistical analyses. These were days in which all groups received treatment, a sufficient number of cats were available based on the sample size calculation, and cats did not undergo sedation. Mean \pm SD intra-gastric pH for cats receiving twice daily (Group 1) or twice daily every second day (Group 2) famotidine at days 0, 1, 13, and 15 are listed in Table 1. No significant period effects were observed for mean pH or MPT intra-gastric pH ≥ 3 and ≥ 4 , thereby indicating that the period of 7 weeks between treatment phases was sufficient ($P = .14$, $P = .43$, and $P = .22$, respectively). The MPT intra-gastric pH ≥ 3 and pH ≥ 4 on baseline day 0 was $21\% \pm 4.0\%$ and $16\% \pm 2.9\%$ for Groups 1 and 2, respectively, and no significant differences were found between treatment groups ($P = .43$ and $P = .42$, respectively).

Significant treatment group by time interactions considering days 1 and 13 were observed for mean intra-gastric pH, MPT intra-gastric pH ≥ 3 and pH ≥ 4 ($P = .009$, $P = .02$, $P = .005$, respectively). Post hoc analyses identified a significant decrease in mean intra-gastric pH of 1.5 on day 13 compared to day 1 for cats in Group 1 ($P = .001$). The MPT intra-gastric pH ≥ 3 on days 1-3 and 11-13 (shown in Figure 2) highlight the decrease in intra-gastric pH over time within Group 1. A 31% decrease in MPT intra-gastric pH ≥ 3 and a 27% decrease for untransformed MPT intra-gastric pH ≥ 4 between days 1 and 13 ($P = .0007$ and $P = .0008$, respectively) were observed for Group 1. No significant differences were found in mean intra-gastric pH ($P = .90$) and MPT intra-gastric pH ≥ 3 and ≥ 4 ($P = .84$ and $P = .78$, respectively) on treatment day 13 compared to day 1 in Group 2. On days in which

TABLE 1 Mean \pm SD intra-gastric pH in cats receiving twice daily (Group 1) or twice daily every other day (Group 2) famotidine

	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)
Day 0	2.2 \pm 1.2 (n = 16)	2.0 \pm 0.06 (n = 16)
Day 1	3.7 \pm 1.3 (n = 16)	3.0 \pm 1.0 (n = 16)
Day 13	2.2 \pm 0.9 (n = 13)	2.9 \pm 1.0 (n = 15)
Day 15	1.7 \pm 0.6 (n = 7)	1.9 \pm 0.6 (n = 11)

No significant differences were observed between treatment groups on day 0 ($P = .56$). There was a marginally significant difference in mean intra-gastric pH between treatment groups on day 1 ($P = .03$). Mean intra-gastric pH was significantly decreased on day 13 compared to day 1 in Group 1 ($P = .001$) but not in Group 2 ($P = .90$). There was a marginal significant difference ($P = .05$) in mean intra-gastric pH between groups on day 13.

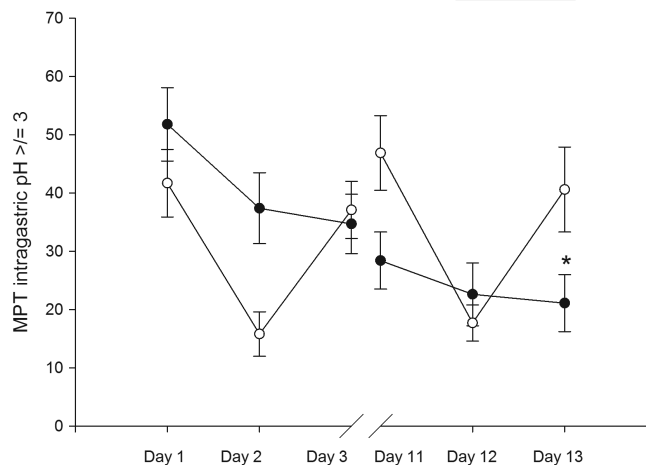


FIGURE 2 Mean percentage time (MPT) for intra-gastric pH ≥ 3 in cats receiving famotidine twice daily (Group 1; closed circles) and twice daily every other day (Group 2; open circles) on days 1-3 and 11-13. Data is reported on days for which a minimum of 13 cats were available for measurement (Group 1: day 0-3, n = 16, day 11-12: n = 15, day 13: n = 13; Group 2: day 0-1: n = 16, day 2-3: n = 14, day 11-13: n = 15). Days 2 and 12 are nontreatment days for Group 2.* MPT intra-gastric pH ≥ 3 was significantly decreased on day 13 compared to day 1 in Group 1 ($P = .0007$) but not in Group 2 ($P = .84$). There was a significant difference between groups on day 13 ($P = .03$)

cats did not receive treatment (eg, days 2 and 12) in Group 2, mean intra-gastric pH decreased (Figure 2). Mean pH and MPT intra-gastric pH ≥ 3 and ≥ 4 for all groups on days 1 and 13 are shown in Figure 3.

Regarding statistical comparisons between Groups 1 and 2, interaction post hoc tests identified a marginally significant difference in mean intra-gastric pH between treatment groups on day 1 ($P = .03$) but not for MPT intra-gastric pH ≥ 3 and ≥ 4 ($P = .15$ and $P = .30$). Significant differences were found between Groups 1 and 2 observed on day 13 for both MPT intra-gastric pH ≥ 3 and 4 ($P = .03$ and $P = .005$, respectively) but not on day 1. When comparing between treatments exclusively on day 13, a marginal significant difference in mean intra-gastric pH was observed ($P = .05$). This resulted in an overall mean decrease in pH of 0.75 in Group 1 compared to Group 2.

3.3 | Serum gastrin concentrations

The reference range for serum gastrin concentration in cats was established as <10.0 - 39.5 pg/dL.¹³ Serum gastrin concentrations (Table 2) increased significantly across time regardless of treatment received ($P < .0001$). Post hoc tests identified significant differences between baseline (day 0) concentrations and those on treatment days 2 ($P < .0001$) and 11 ($P = .0002$). No significant difference was found between or within treatments on days 2 or 11 ($P = .59$). No carryover effects were observed for serum gastrin concentrations (ie, no significant difference was found between treatment groups on day 0; $P = .87$).

3.4 | Rebound hyperacidity

When available (n = 7, Group 1; n = 11, Group 2), data on day 15 were compared to baseline (day 0) to evaluate for rebound gastric hyperacidity after cessation of famotidine administration. No significant

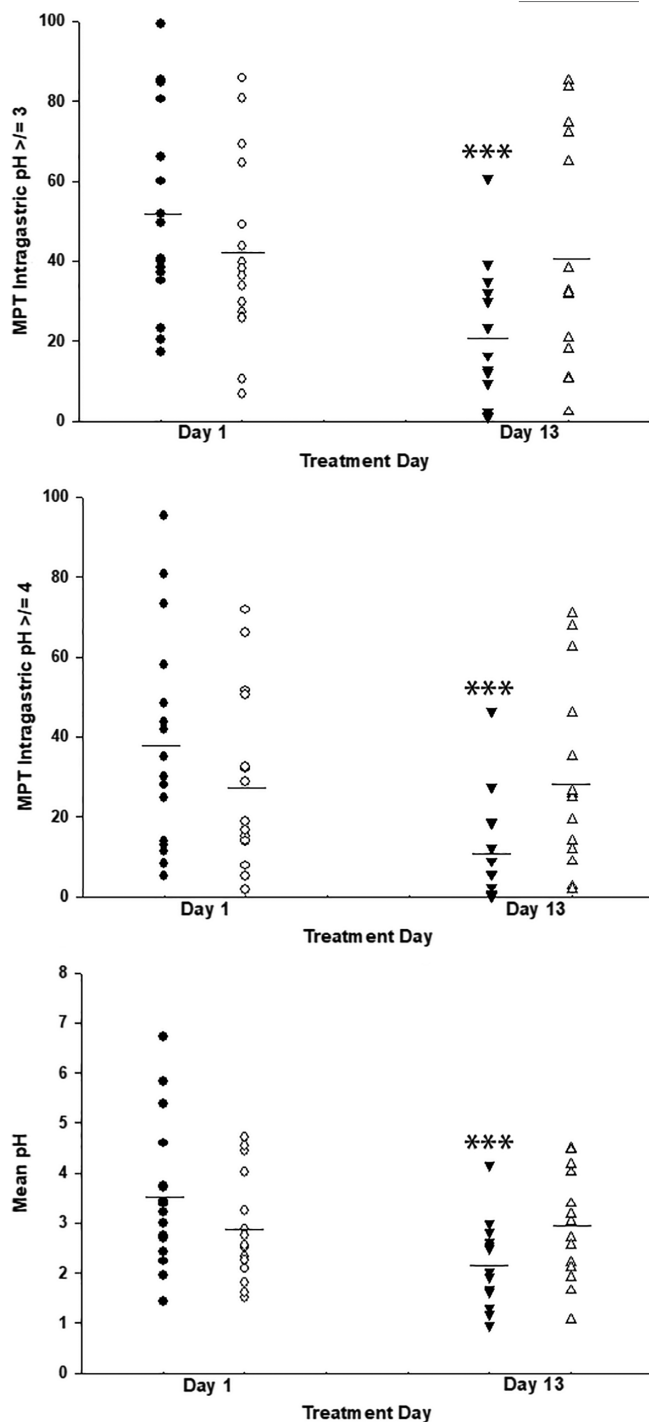


FIGURE 3 Scatterplot of individual cat data comparing mean percent time (MPT) ≥ 3 and ≥ 4 and mean intragastric pH with twice daily (Group 1; closed shapes) and twice daily every second day (Group 2; open shapes) famotidine administration. The horizontal line corresponds to the mean. The number of cats in Group 1 on days 1 and 13 are 16 and 13, respectively, and the number of cats in Group 2 on days 1 and 13 are 16 and 15, respectively. ***Group 1 day 1 compared to day 13: Mean intragastric pH ($P = .001$); MPT intragastric pH ≥ 3 ($P = .0007$); MPT intragastric pH ≥ 4 ($P = .0008$)

differences were observed on day 15 compared to day 0 for either group with regard to mean pH ($P = .12$ for Group 1; $P = 0.95$ for Group 2), MPT intragastric pH ≥ 3 ($P = .11$ for Group 1; $P = .30$ for Group 2), or MPT intragastric pH ≥ 4 ($P = .28$ for Group 1; $P = .18$ for Group 2).

TABLE 2 Untransformed mean \pm SD serum gastrin concentrations in cats receiving famotidine twice daily (Group 1) or twice daily every other day (Group 2)

	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)
Day 0	22.4 \pm 27.3 (n = 16)	17.3 \pm 7.7 (n = 16)
Day 2	81.2 \pm 63.7 (n = 16)	94.4 \pm 100 (n = 16)
Day 11	64.9 \pm 51.8 (n = 15)	52.8 \pm 39 (n = 15)

Statistical comparisons were performed with data from days 0, 2, and 11. Significant differences in gastrin are observed between days 0 and 2 ($P < .0001$), days 0 and 11 ($P = .0002$), but not between days 2 and 11 ($P = .59$)

3.5 | Adverse events

Famotidine was well tolerated during each treatment period. No changes in activity or disposition were observed. The absolute number of episodes in which cats ate $<50\%$ of offered food was 108 (Group 1) and 117 (Group 2). The absolute number of vomiting episodes was 24 (Group 1) and 8 (Group 2). One animal vomited several times when receiving twice daily treatment (13 of reported 24 instances). The majority of these vomiting episodes occurred in the middle of the treatment (days 3-9) and did not occur on days in which statistical analyses for pH were performed. None of these episodes occurred immediately after medicating, and no medications were observed in the vomitus. The absolute number of episodes the mean fecal scores were >4 were 13 (Group 1) and 11 (Group 2). One cat inadvertently missed half of a dose of famotidine on day 2 in Group 1. Data from this day was not included. One cat was excluded from the study early because of its fractious temperament and inability to receive famotidine consistently. This cat's data was included for statistical analysis on day 1 for both groups, but a complete data set was not available for comparison on day 13. Neither inclusion nor exclusion of this cat impacted the results.

4 | DISCUSSION

We evaluated the effect of twice daily (Group 1) and twice daily every second day (Group 2) oral famotidine administration on intragastric pH in cats to determine if a diminished acid suppressing effect, or tolerance, develops over time. Maintaining the MPT intragastric pH ≥ 3 and ≥ 4 for approximately 75% and 67% of the day has been demonstrated to predict tissue healing in human patients with duodenal ulceration and acid-induced esophagitis, respectively, and thus were used, in addition to mean intragastric pH, for comparative analyses.^{15,16} In our study, MPT intragastric pH ≥ 3 and pH ≥ 4 on baseline day 0 was similar to baseline data for the placebo group in a previous study of famotidine administration in cats.¹ Cats in Group 1 had a significant decrease in mean intragastric pH and MPT intragastric pH ≥ 3 or ≥ 4 on treatment day 13 compared to day 1. In Group 1, famotidine administration resulted in a MPT intragastric pH ≥ 3 of 52% and an MPT intragastric pH ≥ 4 of 38% on day 1. By day 13, these had decreased to 21% and 11%, respectively. Therefore, famotidine

administration did not meet the clinical acid-suppressing goals for the treatment of acid-related disorders on day 1 nor over time in Group 1. This finding of diminished famotidine efficacy is consistent with a previous study of twice daily oral famotidine administration over 7 days in healthy cats.¹ This effect might occur earlier than day 13. However, statistical analyses were not performed before this time because of the effect of sedation and fasting on gastric pH on day 11 and lack of a large enough sample size on days earlier than day 11. On day 1, there was a marginally significant difference in mean intragastric pH but not MPT pH ≥ 3 or 4, meaning this finding is likely not clinically relevant.

There were no significant differences in mean intragastric pH and MPT intragastric pH ≥ 3 and ≥ 4 on day 13 compared to day 1 in Group 2. Group 2 cats had an MPT intragastric pH ≥ 3 of 41% on day 1 compared to 40% on day 13 and a MPT intragastric pH ≥ 4 of 27% on day 1 and 13. Thus, these results suggest that the development of tolerance is dependent on daily administration of the drug. It is widely accepted that PPIs are the treatment of choice for the medical management of upper GI ulceration in dogs and cats.¹⁻³ Twice daily every second day administration of famotidine provides weak and intermittent acid suppression, does not meet the aforementioned pH goals, and also is not recommended for acid-related disorder treatment. The benefit of "as needed" famotidine administration in disease states with waxing and waning clinical GI signs, such as chronic enteropathies, CKD, or bilious vomiting, is unknown. In people, famotidine is recommended when fast-acting symptomatic relief is the main clinical goal.⁴ Gastric hyperacidity was not observed in a recent study evaluating cats with mild to moderate CKD.¹² However, clinical trials evaluating the effect of acid suppressants in cats with CKD, especially in advanced stages, have not been published. Many veterinarians believe that famotidine administered as needed improves clinical signs, such as vomiting and hyporexia in cats with CKD, but a scientific basis for how and if this occurs requires further investigation. To our knowledge, pharmacokinetic studies of famotidine in cats have not been reported. Famotidine undergoes active renal tubular excretion in humans and dogs.^{17,18} Thus, a decrease in the dosage or frequency of famotidine administration is recommended in patients with renal impairment because of a 7- to 10-fold prolongation in elimination half-life and the potential for mental deterioration after IV administration.^{19,20} Decreased renal excretion would necessitate a decrease in the frequency of famotidine administration in cats with CKD. Thus, once daily or twice daily every second day administration of famotidine, if a beneficial effect of weak acid suppression can be demonstrated, might be a good option. However, studies investigating if tolerance occurs with twice daily every second day administration in cats with decreased renal excretion also are needed.

Serum gastrin concentrations significantly increased with famotidine, regardless of treatment frequency. By day 11, gastrin concentrations had not returned to baseline. This finding is in contrast to dogs, in which serum gastrin concentrations transiently increased but returned to baseline by day 12 of famotidine administration.²¹ Based on these data, we believe that famotidine still may be imparting an effect, albeit negligible, on gastric pH in cats on day 11. The effect of sedation, as performed on days 0 and 11, on serum gastrin concentrations is unknown and warrants further study.

Rebound acid hypersecretion is defined as gastric acid secretion above the pretreatment baseline after withdrawal of acid suppressant treatment.^{22,23} In people, H2RAs induce a short-lived and clinically insignificant RAH compared to PPIs.²² To our knowledge, RAH has not been evaluated previously with H2RA administration in cats. We did not detect overt RAH after abrupt cessation in either group based on the analysis of baseline day 0 to day 15 data. However, we did not measure gastric acid secretion and cannot definitely say that abrupt cessation of famotidine does not induce RAH. Moreover, our evaluation for RAH was underpowered because most pH capsules had passed out of the stomach by day 15 ($n = 9$, Group 1; $n = 5$, Group 2). An additional study with a larger sample size would be required to confirm our findings.

In conclusion, ours is the first study to demonstrate that tolerance occurs over time with oral famotidine administration in healthy colony cats at the dosages studied. This effect appears to be dependent on dose or daily administration of famotidine. Additional studies are needed to determine if the tolerance phenomenon develops in client-owned cats with metabolic, inflammatory, and neoplastic diseases. However, until such studies are performed, we do not recommend long-term, twice daily oral administration of famotidine in cats because it loses its acid-suppressing effect over time.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION


The IACUC at the University of Tennessee approved the protocol for this study (Approval # 2501-0117).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Parkinson S, Tolbert K, Messenger K, et al. Evaluation of the effect of orally administered acid suppressants on intragastric pH in cats. *J Vet Intern Med.* 2015;29:104-112.
2. Sutalo S, Ruetten M, Hartnack S, et al. The effect of orally administered ranitidine and once-daily or twice daily orally administered omeprazole on intragastric pH in cats. *J Vet Intern Med.* 2015;29:840-846.
3. Tolbert K, Bissett S, King A, et al. Efficacy of oral famotidine and 2 omeprazole formulations for the control of intragastric pH in dogs. *J Vet Intern Med.* 2011;25:47-54.
4. Huang JQ, Hunt RH. Pharmacological and pharmacodynamic essentials of H-2-receptor antagonists and proton pump inhibitors for the practising physician. *Best Pract Res Clin Gastroenterol.* 2001;15:355-370.
5. Markovich JE, Freeman LM, Labato MA, et al. Survey of dietary and medication practices of owners of cats with chronic kidney disease. *J Feline Med Surg.* 2015;17:979-983.
6. Gould E, Klos J, Price J, Harris T, Vaden S, Tolbert MK. Retrospective analysis of the effect of acid-suppressant therapy on clinicopathologic parameters of cats with chronic kidney disease. *J Feline Med Surg.* 2018;20:520-527.
7. Tolbert MK, Graham A, Odunayo A, et al. Repeated famotidine administration results in a diminished effect on intragastric pH in dogs. *J Vet Intern Med.* 2017;31:117-123.
8. Balcomb CC, Heller MC, Chigerwe M, Knych HK, Meyer AM. Pharmacokinetics and efficacy of intravenous famotidine in adult cattle. *J Vet Intern Med.* 2018;32:1283-1289.
9. Takahashi M, Katayama Y. Reversal of the tolerance phenomenon by the intermittent administration of a histamine H2-receptor antagonist. *J Gastroenterol Hepatol.* 2010;25:1493-1497.
10. Komazawa Y, Adachi K, Mihara T, et al. Tolerance to famotidine and ranitidine treatment after 14 days of administration in healthy subjects without *Helicobacter pylori* infection. *J Gastroenterol Hepatol.* 2003;18:678-682.
11. Gould E, Clements C, Reed A, et al. A prospective, placebo-controlled pilot evaluation of the effect of omeprazole on serum calcium, magnesium, cobalamin, gastrin concentrations, and bone in cats. *J Vet Intern Med.* 2016;30:779-786.
12. Tolbert MK, Olin S, MacLane S, et al. Evaluation of gastric pH and serum gastrin concentrations in cats with chronic kidney disease. *J Vet Intern Med.* 2017;31:1414-1419.
13. Ruhnke I, Suchodolski JS, Schwierk VM, et al. Analytical validation of a commercially available immunoassay for serum gastrin concentrations in cats. *J Vet Intern Med.* 2010;24:753-753.
14. Littell R. *SAS for Mixed Models.* 2nd ed. Cary, NC: SAS Institute Inc; 2006.
15. Bell NJV, Burget D, Howden CW, Wilkinson J, Hunt RH. Appropriate acid suppression for the management of gastroesophageal reflux disease. *Digestion.* 1992;51:59-67.
16. Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression for healing of duodenal ulcers—a model of the relationship between ulcer healing and acid suppression. *Gastroenterology.* 1990;99:345-351.
17. Boom SP, Hoet S, Russel FG. Saturable urinary excretion kinetics of famotidine in the dog. *J Pharm Pharmacol.* 1997;49:288-292.
18. Echizen H, Ishizaki T. Clinical pharmacokinetics of famotidine. *Clin Pharmacokinet.* 1991;21:178-194.
19. Gladziwa U, Klotz U, Krishna DR, Schmitt H, Glockner WM, Mann H. Pharmacokinetics and dynamics of famotidine in patients with renal failure. *Br J Clin Pharmacol.* 1988;26:315-321.
20. Yoshimoto K, Saima S, Echizen H, et al. Famotidine-associated central nervous system reactions and plasma and cerebrospinal drug concentrations in neurosurgical patients with renal failure. *Clin Pharmacol Ther.* 1994;55:693-700.
21. Mordecai A, Sellon RK, Mealey KL. Normal dogs treated with famotidine for 14 days have only transient increases in serum gastrin concentrations. *J Vet Intern Med.* 2011;25:1248-1252.
22. Waldum HL, Qvigstad G, Fossmark R, Kleveland PM, Sandvik AK. Rebound acid hypersecretion from a physiological, pathophysiological and clinical viewpoint. *Scand J Gastroenterol.* 2010;45:389-394.
23. Fossmark R, Johnsen G, Johanssen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. *Aliment Pharmacol Ther.* 2005;21:149-154.

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