Repeated Famotidine Administration Results in a Diminished Effect on Intragastric pH in Dogs

M.K. Tolbert, A. Graham, A. Odunayo, J. Price, J.M. Steiner, K. Newkirk, and S. Hecht

Background: Famotidine is an acid suppressant commonly administered to dogs. Prolonged famotidine use in people results in decreased efficacy, but the effect in dogs is unknown.

Hypothesis/Objectives: To compare the effect of repeated oral administration of famotidine or placebo on intragastric pH and serum gastrin in dogs. We hypothesized that famotidine would have a diminished effect on intragastric pH on day 13 compared to day 1.

Animals: Six healthy adult colony Beagles.

Methods: Randomized, 2-factor repeated-measures crossover design. All dogs received oral placebo or 1.0 mg/kg famotidine q12h for 14 consecutive days. Intragastric pH monitoring was used to continuously record intragastric pH on treatment days 1–2 and 12–13. Mean pH as well as mean percentage time (MPT) that intragastric pH was ≥ 3 or ≥ 4 were compared between and within groups by analysis of variance. Serum gastrin was measured on days 0, 3, and 12 for each treatment.

Results: Continued administration of famotidine resulted in a significant decrease in mean pH, MPT ≥ 3, and MPT ≥ 4 ($P < .0001$) on day 12 and 13. This resulted in a mean decrease in pH by 1.63 on days 12 and 13 compared to days 1 and 2. Furthermore, a mean decrease of MPT ≥ 3 and MPT ≥ 4 by 33 and 45% was observed for the same time period, respectively.

Conclusions and Clinical Importance: Continued administration of famotidine results in a diminished effect on intragastric pH in dogs. Caution is advised when recommending long-term, daily oral administration of famotidine to dogs.

Key words: Acid suppressant; Dog; Gastrin; Histamine-2 receptor antagonist.

A cid-related disorders such as gastrointestinal (GI) erosion and ulceration or reflux-induced esophagitis are increasingly recognized in veterinary patients. Although the cause of acid-related disorders is often multifactorial, healing of proximal GI tissue injury is based on sustaining an increased gastric pH. In human patients with acid-related disorders, the mean percentage of time (MPT) that the gastric pH is above 3.0 and 4.0 in a 24-hour period predicts tissue healing.[1,2] Thus, acid suppressant drugs represent the mainstay of the medical treatment of acid-related disorders. Two classes of acid suppressants, proton pump inhibitors (PPIs) such as omeprazole, and histamine-2 receptor antagonists (H2RAs), such as famotidine, are commercially available.

In published studies in healthy dogs and cats, omeprazole has proven to be more effective at raising intragastric pH than famotidine and is often

Abbreviations:

CDAD	*Clostridium difficile*-associated diarrhea
CKD	chronic kidney disease
GI	gastrointestinal
H2R	histamine-2 receptor antagonist
MPT	mean percentage time
PPI	proton pump inhibitor

recommended for the treatment of erosive and ulcerative GI disease.[3–5] Despite this, famotidine continues to be widely used in veterinary medicine and there might be good reasons behind this practice. Unlike omeprazole, famotidine can be given with a full meal, is relatively inexpensive, is thought to have additional tissue healing effects including increased mucus and bicarbonate secretion, and is maximally effective within hours of administration.[6] Moreover, chronic administration of PPIs to dogs and cats might not be without complications. A recent meta-analysis suggested an association between chronic PPI use and development of chronic kidney disease (CKD) in people.[7] Chronic use of PPIs has also been linked to a wide range of adverse effects in people, including an increased risk for the development of community-acquired pneumonia, *Clostridium difficile*-associated diarrhea (CDAD), hypocobalaminemia, and decreased bone mineral content.[8–11] The development of adverse effects depends on the duration of exposure to the drug with some adverse effects occurring within days to weeks (eg, CDAD) and others developing after years of chronic use (eg, hypomagnesemia). Omeprazole administration for 60 days can result in hypergastrinemia, withdrawal-induced rebound gastric acid hypersecretion, and potentially decreased bone mineral content in cats.[12] Additionally, aggressive acid suppression is not always warranted. Therefore,

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famotidine, a weaker acid suppressant associated with fewer adverse effects than PPIs in people, might be a reasonable choice of acid suppression in dogs when prolonged or less potent acid suppression is desired. However, the efficacy of prolonged famotidine use has not been explored in dogs. Repeat famotidine administration might lead to diminished efficacy in dogs. The acid suppressing effects of famotidine and other H2RAs in humans can decrease with continued administration perhaps because of a reduction in the degradation of parietal cell H2-receptors over time.[6,13] In people, this effect occurs in as little as 8 days of continuous oral treatment.[14–16] Recognition of this phenomenon in dogs is needed to create successful acid suppressant therapy guidelines. In a study designed to evaluate serum gastrin concentrations in 11 dogs receiving oral famotidine at 0.5 mg/kg twice daily, gastrin was increased on day 3 but returned to normal on day 14 despite continued famotidine administration.[17] Although intragastric pH was not measured in that study, these results suggest a reduction in efficacy over time.

Despite its widespread use, studies have not been undertaken to investigate for a potential for a diminishing acid suppressing effect of famotidine over time in dogs. Accordingly, the objective of this study was to determine whether continued administration of famotidine leads to a reduced effect on intragastric pH in dogs. We hypothesized that famotidine would have a diminished effect on intragastric pH on day 13 compared to day 1.

Materials and Methods

Study Animals

The Institutional Animal Care and Use Committee (IACUC) at the University of Tennessee approved the protocol for this study (Approval# 2456-0516). The subjects of this study were 6 healthy adult Beagle dogs from a research colony at the University of Tennessee (4 neutered and 2 intact males), aged 4.0–5.5 years (median, 5 years), and weighing 10.5–15.3 kg (median, 13.0 kg). All dogs lacked clinical signs of GI disease and were deemed healthy on the basis of review of history and available historical blood work as well as normal physical examination, normal baseline blood work (ie, PCV, serum chemistry, serum cobalamin and folate, venous blood gas,[a] and urinalysis), and negative fecal examinations by zinc and sugar sulfate centrifugation flotation methods performed at study entry. All dogs were also given 2 doses of a prophylactic broad-spectrum anthelmintic[b] 2 weeks apart before the onset of the study.

Study Design

In a randomized, open label, 2-factor repeated-measures crossover design, all dogs were PO administered placebo (250 mg lactose[c]) q12h or 15 mg famotidine[d] (median, 1.15 mg/kg; range, 0.98–1.42 mg/kg) q12h with their meal. The objective was to dose famotidine as close to 1 mg/kg q12h as possible as this is the standard dose of famotidine used in our hospital for treatment of ulcerative disease. Dogs were randomized to a treatment schedule by a random number generator so that 3 dogs each were randomized to receive famotidine or placebo first. Dogs were medicated and fed[e] at consistent times twice daily. Clinical signs, including change in attitude, appetite, vomiting, number of defecations, and fecal character, were recorded at least twice daily. Feces were graded from 1 to 7 by a standardized fecal scoring system.[f] A washout period of 20 days separated treatment groups, with no medications administered during this time period, to prevent carryover effects.

Intragastric pH Monitoring

One day before the first treatment period (day 0, baseline), dogs were sedated with dexmedetomidine[g] (0.005 mg/kg) and butorphanol[h] (0.4 mg/kg) IV. An IV catheter was placed, and general anesthesia was induced with propofol[i] to effect. General anesthesia was maintained in dogs with sevoflurane[j] in 100% oxygen after endotracheal tube placement. The entire esophagus and stomach were evaluated by endoscopy for any evidence of gross disease. Gastric biopsy samples were obtained by routine gastric endoscopic biopsy. Gastric tissue samples were fixed in 10% buffered formalin, paraffin embedded, sliced in 5-μm sections, stained with hematoxylin and eosin, and assessed by a single board-certified pathologist (KN). After acquisition of biopsies, a pH capsule[k] was placed in the gastric fundus under endoscopic guidance as previously described.[3,18] Before use, all pH capsules and receivers were calibrated as previously described according to manufacturer's instructions.[3] All pH capsules were placed by the same investigator (MKT). The location of each pH capsule was kept consistent in each dog within and 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. On day 12 of both treatment periods as well as baseline (day 0) of the second treatment group, pH capsules were placed by radiographic guidance under sedation with dexmedetomidine and butorphanol, as previously described[12], to eliminate the need for repeated general anesthesia. Briefly, after sedation, dogs were placed in left lateral recumbency. The pH capsule was then blindly introduced transorally into the proximal stomach. We used the recorded length of the delivery device measurement for the first capsule placed endoscopically to place the second capsule in a similar location. For radiographic assessment, location of the capsule with its delivery device in respect to the stomach was evaluated on orthogonal (lateral and ventrodorsal) abdominal radiographs after published criteria for normal radiographic anatomy of the stomach in dogs.[19] Successful placement of the capsule within the fundus was ascertained by visualization of the device in the dorsal part of the stomach (at the level of or slightly dorsal to the esophageal hiatus) on the lateral view, and to the left of midline on the ventrodorsal view which corresponds to reported location of the gastric fundus on abdominal radiographs in dogs (Fig. 1A). The ability to visualize rugal folds in these fasted animals with a small amount of gas and no fluid or solid contents within the gastric lumen further aided in radiographic identification of the fundus. After confirmation of correct positioning, the pH capsule was adhered to the gastric mucosa with vacuum suction and a spring-loaded pin as previously described[3]. The delivery device was removed. Abdominal radiographs were obtained to ensure that the capsule remained firmly adhered in the desired location (Fig. 1B). The sedation was reversed with atipamezole[l] (0.05 mg/kg IM) after each capsule placement.

pH Recordings

Intragastric pH recordings were obtained telemetrically at 6-second sampling intervals for a minimum of 48 hours after capsule placement starting at baseline (day 0) and on treatment days 12. The corresponding data receivers were kept on the front of each dog's run during the data acquisition phase. When the dogs were
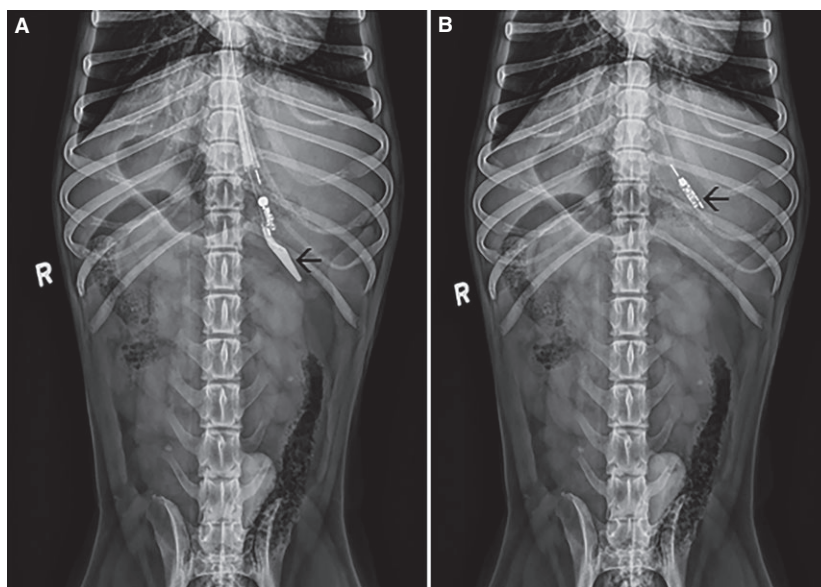
Fig. 1. Ventrodorsal abdominal radiograph confirming adequate radiographic placement of the pH capsule. (**A**) The capsule and its associated delivery device (arrow) can be visualized near the air-filled gastric fundus. (**B**) Ventrodorsal abdominal radiograph from same dog after removal of delivery device. The adhered capsule (arrow) can be visualized in the same location as in (**A**).

walked or given time for play, the receivers remained with the caretaker within 6 feet of the dogs. pH data were uploaded to the computer by manufacturer software[m] every 24 hour for each monitoring period. After data upload, data from the receiver were cleared and the receiver was used to obtain data for the next 24 hour. Data from day 0, a nontreatment day, was excluded from analysis. The mean pH and MPT that intragastric pH was ≥3 and ≥4 were calculated by the manufacturer software.

Serum Gastrin Measurements

At baseline and on treatment days 3 and 12, 3 mL of blood was obtained via jugular venipuncture. Serum was collected from blood tubes after centrifugation at $250 \times g$ 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 gastrin concentrations. Serum gastrin concentrations were measured with an automated chemiluminescent, enzyme-labeled immunometric assay[n] as previously described.[20]

Statistical Analysis

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 was ≥3 and ≥4 for treatment, time (day of treatment), and period differences. To be conservative, a value of 9.9 was assigned to all gastrin data that was below the limit of detection (<10 ng/L). Serum gastrin concentration data were then rank transformed and analyzed by repeated-measures crossover ANOVA to evaluate for treatment, time, and period differences. Heterogeneous variance structures were incorporated into each model, for both pH and gastrin data, to adjust for unequal between subjects treatment variances.[21] For pH data, the interaction of treatment and time was tested to explain, when significant differences were found, how each pH measure changed over time, while dogs were under the effects of each treatment. To accomplish this, a single-factor within-subjects repeated-measures ANOVA was established. In

each model, a contrast was developed to see whether mean values for days 1 and 2 were statistically different than mean values for days 12 and 13 for each pH measure under each treatment. A Shapiro–Wilk W 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 were met. Heterogenous variances were incorporated during model development.[21]

Results

Gastroscopy and Evaluation of Gastric Tissue Samples

Gastroesophageal endoscopic evaluation did not reveal abnormalities of the gastric mucosa in any dog. Histologic examination of gastric tissue samples revealed the presence of large (4–10 μm in length; most >5 μm), helical-shaped bacteria, presumed to be *Helicobacter* spp., on the luminal surface and in the superficial portions of the gastric glands in all dogs. In 3 of the 6 dogs, mild lymphoplasmacytic gastritis (20–50 lymphocytes and plasma cells per 400× field) was noted. The clinical importance of these mild changes is unknown as there were no GI signs or biochemical abnormalities suggestive of GI disease in affected dogs.

pH Monitoring

A total of 24 of 27 pH capsules were successfully attached to the fundic mucosa. On 2 occasions (one with endoscopic guidance and one with radiographic guidance), the pH capsule failed to deploy from the delivery device. This was thought to be attributable to a malfunction of the delivery device itself. On the 3rd occasion, by which placement of the capsule was attempted with radiographic guidance, capsule

attachment was unsuccessful because food particles obstructed the capsule's suction well. In all 3 cases, a new pH capsule was placed in the gastric fundus without complications. With respect to the adhered capsules, on 2 occasions, the Bravo pH capsule detached and exited the stomach before the end of the pH monitoring period. This occurred in 1 dog while receiving famotidine on treatment day 2 and one other dog while receiving placebo on treatment day 13. Therefore, data from these dogs were not included in the treatment comparisons on days in which the data were not available. In 5 dogs receiving famotidine and 3 dogs receiving placebo on day 3 and 3 dogs receiving famotidine and 4 dogs receiving placebo on day 14 of treatment, capsules remained in the stomach and, thus, additional data were gathered and described on these days but were not included in statistical comparisons.

Intragastric pH Recordings

The MPT that the gastric pH was ≥3.0 and 4.0 in a 24-hour period was used, in addition to mean intragastric pH, for analyses.[1,2] The mean ± standard error MPT intragastric pH ≥3 and ≥4 as well as mean intragastric pH for dogs receiving famotidine and placebo on days 1–2 and 12–13 are listed in Table 1 and Figures 2 and 3. No significant differences were observed over time for dogs receiving placebo. Dogs receiving famotidine showed a significant decrease ($P < .0001$) in mean intragastric pH, MPT ≥3, and MPT ≥4 on treatment days 12 and 13 as compared to days 1 and 2. This resulted in a mean decrease in intragastric pH by 1.63 on days 12 and 13 when compared to days 1 and 2. Furthermore, a mean decrease of 33 and 45% was observed for MPT intragastric pH ≥3 and pH ≥4, respectively, over the same time period. This resulted in famotidine achieving the goals established for the treatment of ulcerative and esophageal reflux diseases on days 1 and 2 but not meeting these goals in all dogs on days 12 and 13. Moreover, in dogs where data were available (n = 5; Fig. 4), mean intragastric pH as well as MPT intragastric pH ≥3 and pH ≥4 decreased on day 3. As a result, MPT intragastric pH ≥3 and pH ≥4 also did not meet goals for increase in pH on day 3. When comparing famotidine versus placebo, famotidine was only significantly different from all days of placebo for MPT intragastric pH ≥3 on days 1 and 2

Fig. 2. Efficacy of famotidine over time as assessed by mean percent time (MPT) intragastric pH was ≥3. Closed circles represent the MPT (±SE) pH ≥3 for dogs receiving famotidine. Open circles represent the MPT (±SE) pH ≥3 for dogs receiving placebo. ***Values were significantly decreased compared to days 1 and 2 of famotidine.

Fig. 3. Efficacy of famotidine over time as assessed by mean percent time (MPT) intragastric pH was ≥ 4. Closed circles represent the MPT (±SE) pH ≥4 for dogs receiving famotidine. Open circles represent the MPT (±SE) pH ≥4 for dogs receiving placebo. ***Values were significantly decreased compared to days 1 and 2 of famotidine.

($P = .008$). Significant differences for the treatment by time interactions were observed for mean intragastric pH ($P = .0114$) and MPT intragastric pH ≥4 ($P = .0039$); however, all main effects were also only significant from all days of placebo for mean intragastric pH and MPT intragastric pH ≥4 on famotidine treatment days 1 and 2. There were no significant differences in mean intragastric pH, MPT intragastric pH ≥3, and ≥4 between famotidine and placebo on days 12 and 13. There were no significant period effects, thereby indicating that the washout period of 20 days was sufficient. There were no significant differences in regard to the effect of famotidine on mean intragastric pH, MPT intragastric pH ≥3, and ≥4 between dogs with gastritis and dogs without gastritis.

Serum Gastrin Concentrations

Mean serum gastrin concentrations corresponding to each treatment and day are shown in Figure 5. All

Table 1. Mean (±SE) intragastric pH in dogs receiving placebo or famotidine.

	Placebo (Mean ± SE)	Famotidine (Mean ± SE)
Day 1	2.8 ± 0.39 (n = 6)	4.9 ± 0.27 (n = 6)
Day 2	2.0 ± 0.39 (n = 6)	4.8 ± 0.29 (n = 5)
Day 12	2.3 ± 0.39 (n = 6)	3.4 ± 0.27 (n = 6)***
Day 13	2.5 ± 0.42 (n = 5)	3.1 ± 0.27 (n = 5)***

Mean intragastric pH was significantly different (***$P < .0001$) on days 12 and 13 as compared to days 1 and 2 after famotidine treatment.
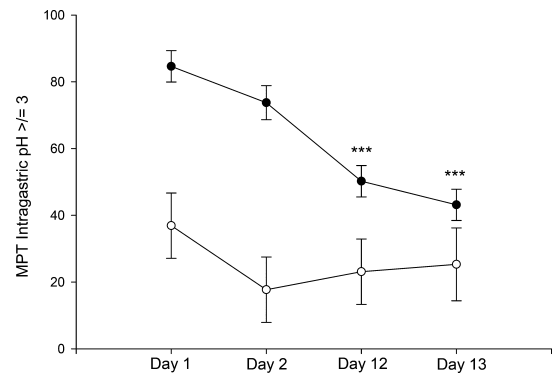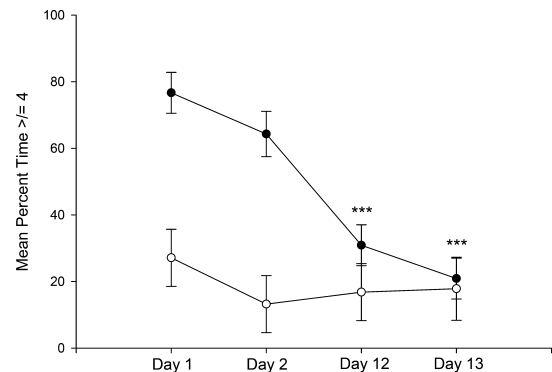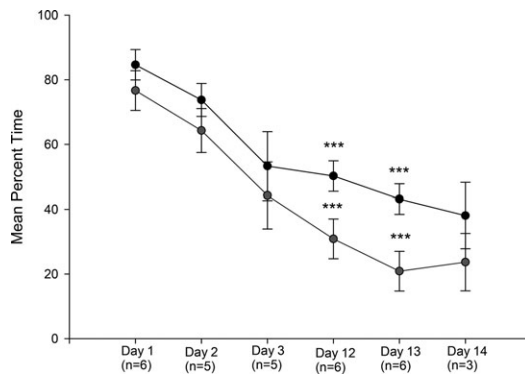
Fig. 4. Mean (±SE) percent time intragastric pH was ≥3 (black line) and ≥4 (gray line) in dogs receiving famotidine on days 1–3 and 12–14. Intragastric pH is noted to decrease beginning on day 3. Statistical comparisons were only made between days 1–2 and 12–13. ***Values were significantly decreased compared to days 1 and 2 of famotidine.
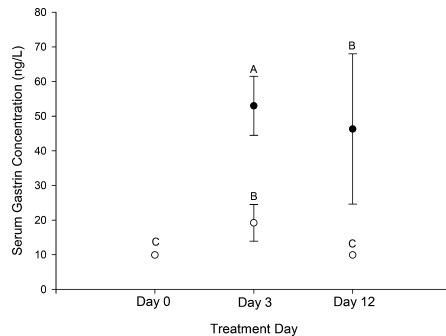

Fig. 5. Untransformed mean (± SE) serum gastrin concentrations in dogs receiving placebo or famotidine. A value of 9.9 was assigned to all gastrin data that were below the limit of detection (<10 ng/L). Closed circles represent the famotidine group. Open circles represent the placebo group. Different letters demonstrate values that were significantly different from each other. All gastrin concentrations were significantly different from one another across all days within the famotidine group.

dogs had gastrin concentrations below the limit of detection on both baseline days. The main effects for gastrin were significantly different across treatment ($P = .016$) and time ($P < .001$). Treatment by time interactions were marginally significant ($P = .06$). Within the famotidine group, all gastrin concentrations were significantly different from one another across all days. Famotidine administration resulted in an increase in serum gastrin in all dogs on day 3. However, gastrin concentrations from 4 of 6 dogs, that were above the upper limit of the reference interval (RI: <27.8 ng/L) on day 3 of famotidine treatment, declined to below upper limit of the RI on day 12. In the remaining 2 dogs, gastrin concentrations stayed above the upper limit of the RI on day 12 of famotidine treatment despite a dramatic decrease in their mean intragastric pH (2.78 and 2.83, respectively) and MPT intragastric pH ≥3 (42.3 and 41.6) and ≥4 (19.6 and 14.4) compared to day 1 of treatment (mean pH: 5.36

and 5.09; MPT pH ≥3: 84.8 and 82.9; MPT pH ≥4: 77.0 and 73.5). Rank transformed mean serum gastrin concentration was significantly different on placebo treatment day 3 compared to days 0 and 12, but was still below the upper limit of the RI. There were no differences in serum gastrin at any time point between dogs with and without gastritis.

Adverse Events

All treatments were well tolerated during each treatment period. No changes in activity or disposition were noted. Adverse events were infrequent. Only 3 vomiting episodes occurred, 1 episode in 1 dog receiving famotidine on day 1 and 1 episode in both treatment groups on days 12–13. The mean fecal scores on days 1 and 2 of famotidine and placebo treatment were 4.5 and 3.4, respectively. The mean fecal scores on days 12 and 13 of famotidine and placebo treatment were 3.7 and 3.7, respectively.

Discussion

In the present study, we evaluated the effect of repeated oral administration of famotidine or placebo on intragastric pH and serum gastrin concentrations in dogs to determine whether famotidine has a diminished acid suppressing effect over time in dogs. Our results demonstrate that dogs receiving famotidine had significant decreases in mean intragastric pH and MPT the intragastric pH was ≥3 and ≥4 on treatment days 12 and 13 as compared to days 1 and 2. In contrast, there were no significant differences in these variables when dogs received placebo for the same time period. The pH goals for the treatment of duodenal ulceration and gastroesophageal reflux disease in humans are to maintain an intragastric pH at or above 3 for at least 75% of the day and a pH at or above 4 for at least 67% of the day, respectively.[1,2] On day 1 of treatment, famotidine administration resulted in excellent gastric acid suppression in our study dogs, achieving a MPT intragastric pH ≥3 and pH ≥4 of 85 and 77%, respectively. On day 2, famotidine administration achieved a MPT intragastric pH ≥3 and ≥4 of 74 and 64%, respectively. By days 12 and 13, however, the gastric acid suppressing effects of famotidine declined significantly and failed to meet either pH goal for pH increase for humans in all dogs. Indeed, on treatment days 12 and 13, there were no significant differences in mean intragastric pH, MPT intragastric pH ≥3, and ≥4 between famotidine and placebo. Moreover, data from 5 dogs receiving oral famotidine suggest that there was already decreased control of gastric acidity on day 3 of treatment. For the most part, serum gastrin concentrations mirrored those of intragastric pH with serum gastrin concentrations being undetectable at baseline, increasing significantly on day 3, and falling by day 12 of famotidine treatment. These results suggest that famotidine might be a good treatment for short-term control of clinical signs or prophylactic therapy but that the efficacy of famotidine decreases over time.

It is unknown if these findings with oral famotidine can be extrapolated to prolonged administration of parenteral forms of famotidine in dogs. However, studies in human subjects suggest that the effect of tolerance occurs even more rapidly, in as short as 12–72 hours, when famotidine is administered IV.[22,23] More studies are needed to determine whether tolerance develops in dogs with repeated intravenous administration of famotidine.

In this study, we chose to investigate oral doses of 1.0 mg/kg q12h as this is the standard dose of famotidine used in our hospital for the treatment of ulcerative disease when a proton pump inhibitor cannot be used. We cannot say if lower doses of famotidine would have also resulted in tolerance in dogs, however, based on work done in people, the authors believe that lowering the dose would still result in tolerance. For example, tolerance developed in people treated with doses as low as 40 mg of famotidine at night and with a variety of doses of ranitidine (150 mg at night, 300 mg at night, and 150 mg twice daily).[24] Moreover, previous work evaluating the effect of lower doses of famotidine (1.0 mg/kg/d) on gastrin concentrations in dogs demonstrated that serum gastrin concentrations normalized within 7–14 days of treatment despite continued famotidine administration. Although more work is needed, this work might suggest that lowering the dose of famotidine would not mitigate induction of tolerance in dogs.[17,25]

Radiographic guidance to place pH capsules was used in this study, as reported in cats.[12] The procedure was quick and easy to perform under sedation and obviated the need for the use of general anesthesia for pH capsule placement in the gastric fundus. The option to place pH capsules with sedation might allow for pursuit of continuous esophageal and gastric pH monitoring in patients where general anesthesia is not feasible or is ill-advised.

This study included a small group of dogs with no known history, physical examination, or biochemical evidence of GI disease. However, 3 of the 6 study dogs had histopathologic evidence of mild lymphoplasmacytic gastritis. The importance of this finding is uncertain given that these dogs were free of clinical signs of disease; however, this emphasizes the importance of the crossover design for pharmacologic studies where each dog serves as its own control. Despite this, the 3 dogs with subclinical gastritis responded similarly to those without gastritis. pH data from all dogs, both with and without gastritis, demonstrated a decreased acid suppressing effect with repeated famotidine administration over time. Moreover, there were no significant differences observed in regard to the effect of famotidine on mean intragastric pH, MPT intragastric pH ≥3, and ≥4 between dogs with and without gastritis. Additional studies are needed to determine whether these results are also observed in dogs with clinical disease that warrants acid suppression therapy.

In conclusion, these results suggest that famotidine loses efficacy as an acid suppressant over time when administered twice daily in dogs. Thus, caution is advised when recommending long-term oral administration of famotidine in dogs.

Footnotes

[a] Stat Profile® pHOx® Ultra, Nova Biomedical©, Waltham, MA

[b] Nemex®, Zoetis, Florham Park, NJ

[c] 250 mg lactose encapsulated in size #3 gelatin capsule, Spectrum Chemical Mfg Corp, Gardena, CA

[d] 20 mg famotidine tablets from Alembic Pharmaceuticals Limited, Gujarat, India

[e] Purina One® SmartBlend® Lamb & Rice Formula, Nestle Purina PetCare Company, St. Louis, MO

[f] Fecal Scoring System, Nestle Purina PetCare Company

[g] Dexdomitor 0.5 mg/mL injection, Orion Pharma, Espoo, Finland

[h] Torbugesic 10 mg/mL injection, Fort Dodge Animal Health, Fort Dodge, IA

[i] PropoFlo 10 mg/mL injection, Fort Dodge Animal Health

[j] SevoFlo, Abbott Laboratories, North Chicago, IL

[k] Bravo pH® capsule with delivery system, Given Imaging, Duluth, GA

[l] Antisedan 5 mg/mL injection, Orion Pharma, Espoo, Finland

[m] Polygram Net Software, Given Imaging, Yoqneam, Israel

[n] Immulite 2000, Siemens Healthcare Diagnostics, Malvern, PA

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