The Effect of Orally Administered Ranitidine and Once-Daily or Twice-Daily Orally Administered Omeprazole on Intragastric pH in Cats

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Background: Gastric acid suppressants frequently are used in cats with acid-related gastric disorders. However, it is not known if these drugs effectively increase intragastric pH in cats.

Objectives: To examine the effects of PO administered ranitidine and omeprazole on intragastric pH in cats and to compare the efficacy of once-daily versus twice-daily dosage regimens for omeprazole.

Animals: Eight domestic shorthair cats.

Methods: Using a randomized 4-way cross-over design, cats were given enteric-coated omeprazole granules (1.1–1.3 mg/kg q24h and q12h), ranitidine (1.5–2.3 mg/kg q12h), and placebo. Intragastric pH was monitored continuously for 96 hours using the Bravo™ system[a], starting on day 4 of treatment, followed by a median washout period of 12 days. Mean percentage of time pH was ≥ 3 and ≥ 4 was compared among groups using repeated measures ANOVA.

Results: Mean ± SD percentage of time intragastric pH was ≥ 3 and ≥ 4 was $67.0 \pm 24.0\%$ and $54.6 \pm 26.4\%$ for twice-daily omeprazole, $24.4 \pm 22.8\%$ and $16.8 \pm 19.3\%$ for once-daily omeprazole, $16.5 \pm 9.0\%$ and $9.6 \pm 5.9\%$ for ranitidine, and $9.4 \pm 8.0\%$ and $7.0 \pm 6.6\%$ for placebo administration. Twice-daily omeprazole treatment significantly increased intragastric pH, whereas pH after once-daily omeprazole and ranitidine treatments did not differ from that of placebo-treated cats.

Conclusion and Clinical Importance: Only twice-daily PO administered omeprazole significantly suppressed gastric acidity in healthy cats, whereas once-daily omeprazole and standard dosages of ranitidine were not effective acid suppressants in cats.

Key words: Acid suppressant; Feline; Omeprazole; Ranitidine.

Acid-related gastric disorders result from an imbalance between gastric acid secretion and gastric acid mucosal defense mechanisms.[1] In humans, gastric acidity plays an important role in gastric ulcer development, and numerous studies have been conducted on the efficacy of PO administration of acid-suppressing drugs.[2] In veterinary medicine, the role of gastric acidity in the pathogenesis of gastric erosive and ulcerative disease has received limited attention, and the most appropriate extent of gastric acid inhibition for acid-related diseases has yet to be determined in small animals.[3] Although gastric erosive disease is commonly suspected in cats, especially in critically ill and stressed cats, it is difficult to confirm because of the inherent invasiveness of gastric mucosal visual inspection. Instead, gastric acid suppressants including histamine-2 receptor antagonists, such as ranitidine or famotidine, and proton pump inhibitors, such as omeprazole, are widely used empirically in this species.

Abbreviations:

PO	per os
PBS	phosphate-buffered saline

Although some information on the antisecretory effects of commonly used acid suppressants (e.g. omeprazole, famotidine, ranitidine) is available for dogs,[4–6] the clinical efficacy of antisecretory drugs in cats is largely unknown. The Existing data on feline gastric pH, derived from studies that used the cat as a model for humans, are difficult to interpret because gastric acid secretion was pharmacologically modified or experiments were carried out in anesthetised cats that had been vagotomized, and pH measurements were determined for only a few hours.[7–10] Despite the relative paucity of studies in cats, acid suppressant medications are commonly used in clinical practice, using dosages extrapolated from studies performed in dogs.[4,5]

The recent introduction of pH monitoring devices such as the Bravo™ system[a] has allowed noninvasive, continuous assessment of intragastric pH over prolonged periods. This technique has been evaluated for extended recordings of intragastric pH in dogs.[4,11] The effects of twice-daily omeprazole versus standard dosages of famotidine on intragastric pH in cats recently have been reported using this new technique. The Results of this study indicated that omeprazole administration provided superior acid suppression compared with famotidine.[12]

The goals of the present study were to determine normal gastric acid profiles in healthy cats, to investigate the effect of omeprazole and ranitidine on intragastric pH in a placebo-controlled study and to compare once-daily and twice-daily dosage regimens for omeprazole. We hypothesized that omeprazole would be superior to ranitidine for achieving a sustained increase in gastric pH and that omeprazole administered twice daily would

provide superior gastric acid control compared with a once-daily dosage regimen.

Materials and Methods

Cats

Eight healthy European shorthair cats (2 intact females, 3 spayed females, 3 intact males), aged 5–6 years (median, 5.7 years) and weighing 4.3–6.8 kg (median, 5.3 kg) with median body condition score of 5/9, were used. All cats were research colony cats from the Institute of Animal Nutrition of our institution. The cats had no clinical signs of gastrointestinal disease for the past 6 months and were deemed healthy based on physical examination findings as well as the results of CBC, serum biochemistry profile and urinalysis. The study was approved by the Cantonal Veterinary Office of Zürich and conducted in accordance with the guidelines established by the Animal Welfare Act of Switzerland (permission no. 527/2013). Permission for the use of animals in our study specified that cats with anorexia, vomiting persisting >24 hours, weight loss exceeding 10% of body weight, or some combination of those would be excluded. During intragastric pH recording periods, pairs of cats were housed in 140 × 105 × 100 cm cages and had daily physical exercise.

Study Design

Using a randomized cross-over design, cats received 1 of the following treatments PO for 7 consecutive days: placebo (empty gelatin capsule)[b] q12h, ranitidine[c] (1.5–2.3 mg/kg; median, 1.9 mg/kg) q12 h, omeprazole[d] (1.1–1.3 mg/kg; median, 1.2 mg/kg) q24h, or omeprazole[d] (1.1–1.3 mg/kg; median, 1.2 mg/kg) q12 h. The goal of treatment was to achieve a dosage of approximately 1 mg/kg for omeprazole, thus, 1 enteric-coated granule containing 1.1 mg omeprazole was given per kg body weight (e.g. a 10 mg omeprazole capsule[d] contained 9 enteric-coated granules each consisting of 1.1-mg omeprazole).[e] The dosage of each drug was consistent among treatments for each cat. All drugs were administered in hard gelatin capsules.[b] To facilitate swallowing, approximately 1 teaspoon of a highly palatable feline food[f] was fed immediately after administration of the capsule. Cats were medicated daily at 6:30 am and 6:30 pm, 30 minutes before a standardized morning and evening meal.[g] The once-daily omeprazole treatment was given in the morning. One of the authors (ŠS) stayed with the cats for a minimum of 45 minutes after treatment to ensure that medication was not regurgitated or vomited. Each treatment period was followed by a median washout period of 12 days (range, 7–24 days). Attitude, appetite, body weight, number of defecations, and fecal consistency were recorded daily. Feces were graded from 1 to 7 (1, very hard; 7, watery) according to a standardized fecal scoring system.[h]

On day 4 of each treatment period, cats were anesthetized after a 12-hour fast for endoscopy-assisted placement of a pH capsule.[a] Cats were premedicated with butorphanol[i] (0.2 mg/kg IM) and medetomidine[j] (5 µg/kg IM), an IV catheter was placed, and general anesthesia was induced with propofol and maintained with isoflurane. Before the first pH capsule placement, routine gastric and duodenal endoscopic biopsy was performed. The biopsy samples were fixed in 10% buffered formalin, embedded in paraffin, cut into 2-µm sections and stained using a routine protocol with hematoxylin and eosin. Gastrointestinal biopsy specimens were assessed by a board-certified pathologist (MR) according to World Small Animal Veterinary Association guidelines.[13] All pH capsules were placed under direct endoscopic guidance by the same investigator (PHK). Immediately before placement, the capsules were calibrated with commercial buffer solutions (pH 1.07 and 7.01)

according to the manufacturer's instructions.[a] A drift of 0.1 pH units was tolerated. All pH capsules were anchored in the fundic area using the supplied delivery system that combined suction and a lock-and-pin mechanism.

The approach for gastric capsule placement was similar to what has been described recently in dogs,[4,11] with the exception that the external vacuum suction (510 mm Hg) applied to the capsule delivery system was decreased from approximately 30 seconds to a median of 20 seconds during the study.[k] After capsule placement, gastric pH recordings were obtained telemetrically at 6-second sampling intervals for 4 days (96 hours). The receiver was kept in close proximity outside of the feline's cage. After acquisition, pH data were uploaded from the receiver to the computer using the manufacturer software.[l] Percentage of time intragastric pH was ≥3 and ≥4 and in 1 of each of 8 categories (pH 0–1, pH 1–2, up to pH 7–8) was calculated by the computer software. Throughout the study, all cats were subjected to visual inspection 4 times daily and were allowed to play in a separate enclosure twice daily. A chaperone (ŠS) was present during these times to entertain the cats and to ensure that the distance to the receiver was adequate.

Investigation of Capsule Dissolution

Because all medications were administered in hard gelatin capsules[b], an experiment was conducted to examine the drug release time at different pH levels. Dissolution of gelatin capsules containing enteric-coated omeprazole granules[d] and ranitidine[c] was examined visually in transparent cups containing 35 ml of phosphate-buffered saline (PBS) buffer solution that was warmed to body temperature (37.5 °C) and had a pH of 1, 2, 3, 4, 5, 6, or 7.

Statistical Analyses

Commercially available software[m] was used for analysis. Repeated measures ANOVA was used to analyze differences among the 4 treatment arms regarding (1) percentage of time intragastric pH was ≥3 and ≥4 during the 96-hour period after pH capsule placement (days 4–7 of treatment), (2) percentage of time intragastric pH was in 1 of 8 pH categories (0–1, 1–2, 2–3, 3–4, 4–5, 5–6, 6–7, 7–8) for days 4–7 of treatment; and (3) adverse effects of treatments by comparing the 7-day mean number of defecations with fecal scores ≥3 and ≥4.

In a second analysis, the different treatment arms were assessed separately and the effect of day was evaluated with repeated measures ANOVA. Assumption of sphericity was examined by Mauchly's test of sphericity and a Bonferroni correction was applied to multiple comparisons. Differences were considered significant at $P < 0.05$.

Results

Cats

All cats were alert and active and had a normal appetite throughout the study. A single episode of vomiting occurred 2 days after Bravo™ capsule placement in 1 of the cats in the twice-daily omeprazole treatment arm.

Assessment of Fecal Scores

The occurrence of fecal scores >3 and >4 did not differ among treatment arms. The median fecal score was 3 for the placebo, 4 for ranitidine, 4 for once-daily treatment with omeprazole, and 4 for twice-daily administration of omeprazole.

Experience with the Bravo™ System[a] in Cats

Overall, 32 Bravo™ capsules were successfully attached to the fundic mucosa. Total procedure times for endoscopy-assisted capsule placement ranged from 5 to 8 minutes, with most procedures taking <5 minutes. In 1 cat, the stomach still contained food, and mucosal capsule attachment was unsuccessful because food remnants obstructed the suction hole. Capsule placement and pH measurement were repeated at a later time point. In 4 cases, the previously attached capsule was still in place at the time of the subsequent pH measurement (Fig. 1). Because endoscopic removal of the capsule with the help of endoscopic foreign body retrieval devices and polypectomy forceps was unsuccessful in the first case, a new capsule was attached next to the other 1 in these 4 cats. No problems were encountered with this approach. Passing of pH capsules through the digestive tract was verified by daily fecal examination in all cats. A total of 2,909 hours and 20 minutes of intragastric pH recording time (equivalent to 1,745,580 pH readings) was obtained. The maximum possible data acquisition was 3,072 hours (96 hours per cat per treatment). Therefore, the overall missing data rate was 5.3%. Missing data were caused by signal interference in the radiotelemetric system, which occurred intermittently in all treatment groups.

Endoscopic and Histologic Assessment of Gastrointestinal Biopsy Samples

Gastroduodenoscopic evaluation was normal in all cats. Histologic examination of endoscopic gastric biopsy samples showed severe colonization of the mucosal surface with spiral-shaped organisms interpreted as gastric *Helicobacter spp.* in all of the cats. There were no concurrent lesions in the mucosa or lamina propria. The villi of the intestine were slender and had normal architecture with a crypt-to-villi ratio of 1:4. The epithelium was normal but in the lamina propria, small clusters of 9–12 neutrophils per high power field (hpf) were observed in 5 cats. The remaining 3 cats had smaller clusters of 4–5 neutrophils per hpf scattered in the lamina propria. The final histologic diagnosis was gastric colonization by *Helicobacter spp.* Duodenal tissue was deemed normal.

Assessment of Capsule Dissolution

The capsules started to swell within 2 minutes of being placed in the PBS buffer solution. Complete disintegration of the capsules and release of the contents occurred within 5 minutes at all pH levels.

Intragastric pH Recordings

With respect to percentage of time intragastric pH was ≥3 and ≥4, twice-daily omeprazole had a significantly greater effect than once-daily omeprazole, ranitidine, and placebo administration. There were no significant differences among the latter 3 treatment arms.

Mean ± SD percentage of time intragastric pH was ≥3 and ≥4 was 67.0 ± 24.0% and 54.6 ± 26.4% for twice-daily omeprazole administration, 24.4 ± 22.8% and 16.8 ± 19.3% for once-daily omeprazole administration, 16.5 ± 9.0% and 9.6 ± 5.9% for ranitidine administration, and 9.4 ± 8.0 and 7.0 ± 6.6% for placebo administration (Fig. 2).

The treatment arms differed with respect to the distribution of intragastric pH over pH categories 1–8 (Fig. 3). For pH category 1–2, twice-daily omeprazole administration differed significantly from the other treatment arms (placebo, $P = 0.02$; once-daily omeprazole, $P = 0.024$; ranitidine, $P = 0.040$). For categories 3–4, 4–5, 5–6, and 6–7, twice-daily omeprazole differed significantly from placebo, and for pH categories 4–5, 5–6, and 6–7, ranitidine differed significantly from placebo. To summarize, intragastric pH ranged widely across all pH categories with all treatments; but twice-daily omeprazole resulted in the largest amount of time intragastric pH was in categories 3–4 to 6–7.

Comparison of treatment days within a given treatment identified a significant increase in intragastric pH between days 4 and 7 only for twice-daily omeprazole ($P = 0.011$ for pH ≥3; $P = 0.044$ for pH ≥4).

Discussion

Although more commonly encountered in dogs, gastric erosive and ulcerative disease can exacerbate a range of gastrointestinal, metabolic, or neoplastic conditions[14] or be a complication of nonsteroidal anti-inflammatory drug administration in cats.[15] Gastric acid suppressants currently are the treatment of choice for

Fig. 1 View of the Bravo™ capsule attached to the feline gastric mucosa. Compared to dogs,[11] comparatively large parts of the gastric mucosa became lodged in the suction well of the capsule.
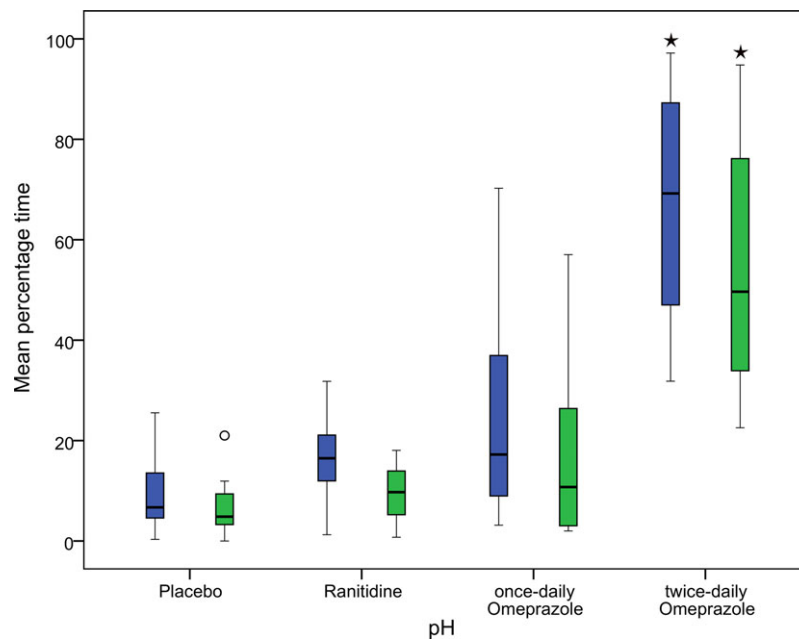
Fig. 2 Comparison of efficacy of various treatments on intragastric pH. Box plots show variation in percentage of time intragastric pH was ≥3 (blue) and ≥4 (green) for 8 cats given placebo, ranitidine, once-daily omeprazole and twice-daily omeprazole. *Results were significantly increased compared with placebo, ranitidine, and once-daily omeprazole ($P = 0.011$ for pH ≥3; $P = 0.044$ for pH ≥4).

these conditions. Because information on the efficacy of antisecretory drugs is scarce in cats,[9,b] the goal of the present study was to compare the effects of PO administered gastric acid suppressants commonly used in cats. Our study clearly demonstrated that twice-daily omeprazole administration provided superior gastric acid suppression compared with a once-daily dosage regimen and with standard dosages of ranitidine and placebo based on percentage of time intragastric pH was ≥3 and ≥4. The conceptual basis for these cut-offs has been explored by meta-analysis of many trials in human medicine, and these cut-offs are now considered ideal for promoting optimal gastrointestinal ulcer healing.[16,17] Comparison of once-daily and twice-daily omeprazole administration was chosen because additional drug administration could pose a substantial problem for sick cats and would likely result in poor owner compliance. A twice-daily dosage regimen used in small animals has been largely extrapolated from studies of humans.[18] A simplified omeprazole suspension (enteric-coated granules suspended in 8.4% sodium bicarbonate) administered to dogs as a bolus through a stomach tube resulted in superior gastric acid suppression over 24 hours compared with once-daily omeprazole.[5] Another study in dogs found that the effect of once-daily administration of reformulated omeprazole paste used in horses for gastric acid secretion waned substantially during 24 hours after administration.[4] It therefore was postulated that a twice-daily dosage regimen was more beneficial. It was surprising that the once-daily dosage of omeprazole in the present study had poor results in cats because comparable omeprazole dosages in dogs yielded a mean percentage of time with intragastric pH ≥3 of 70.2% and ≥4 of 52.3%.[5] Species-specific

differences such as increased *de novo* biosynthesis of proton pumps may account for this difference because restoration of acid secretion is dependent on pump biosynthesis.[18] Delayed gastric release of omeprazole from the gelatin capsule with inadequate intestinal absorption caused by variability in the hardness of the capsule wall[n] was ruled out as a cause of the unexpected low intragastric pH because the capsules were shown to dissolve quickly at all pH levels.

The effects of ranitidine and placebo on intragastric pH did not differ in the present study, which is in contrast to a recent report that PO administered famotidine in cats had better antisecretory efficacy than placebo.[b] Ranitidine and famotidine were shown to have poor antisecretory properties in dogs.[4,5] We anticipated similar results, based on observations that plasma gastrin concentrations did not increase in cats undergoing long-term ranitidine treatment.[9] This indicates that ranitidine has weak antisecretory properties because gastrin release is inhibited by the presence of acid in the stomach by a negative feedback mechanism. Nevertheless, we felt it was important to provide substantial evidence that ranitidine also is a weak acid suppressant in cats and therefore should not be used for treatment of acid-related gastric disorders in cats.

We used enteric-coated omeprazole granules rather than splitting tablets because a dosage of 1 mg/kg can be more easily approximated by administering 1 granule per kg body weight (1 granule contains 1.1 mg omeprazole),[d] which is convenient in small patients. Omeprazole granules are also used in human pediatric patients and when medication must be given through a feeding tube.[19–21] Moreover, it was felt that splitting enteric-coated omeprazole tablets may adversely affect drug efficacy. However, results published during the course
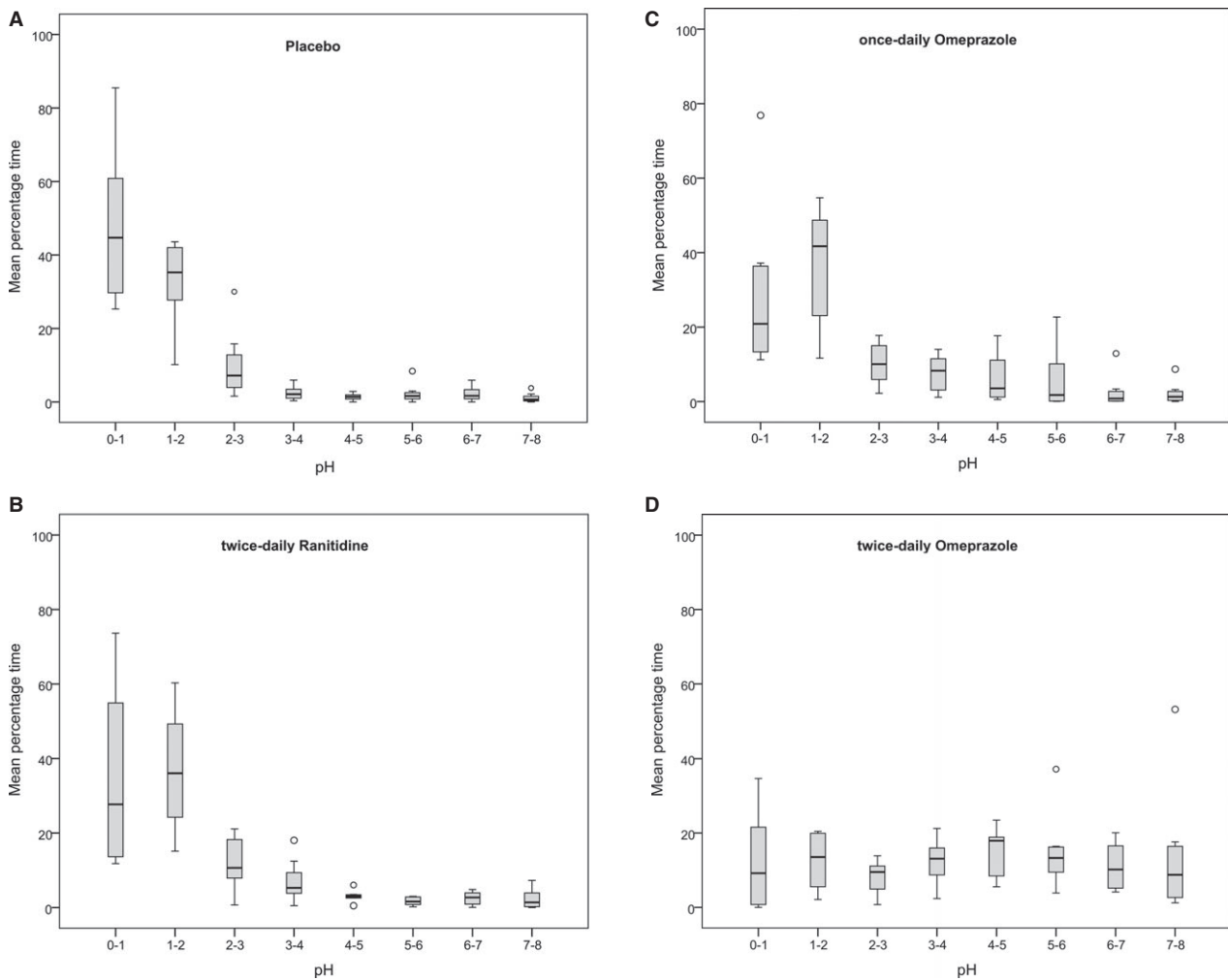
Fig. 3 Box plots representing the intragastric pH distribution for 8 cats receiving placebo (**A**), ranitidine (**B**), once-daily omeprazole (**C**), and twice-daily omeprazole (**D**). Circles represent outliers.

of the present investigation showed that fractionated enteric-coated omeprazole tablets remained effective acid suppressants in cats despite disruption of the enteric coating.[12]

To facilitate swallowing of the capsule, a teaspoon of highly palatable canned feline food[f] was fed immediately after pill administration. Administration of water by syringe usually is recommended after oral drug administration in cats.[22] However, the cats in our study did not tolerate syringe feeding of water, but readily ate the small amount of food[f]. This procedure is likely more practical for owners who administer drugs to their cats at home, and we do not believe that the small amount of food compromised the efficacy of the medication. The administration of omeprazole granules to children in an acidic or alkaline solution or mixed with apple sauce resulted in acid suppression comparable with that of intact capsules in humans.[19,23] Similarly, a study of omeprazole absorption in humans indicated that the area under the curve of omeprazole was similar, and that the total amount of drug absorbed was not affected when the granules were given immediately before or after breakfast.[24]

We chose the Bravo™ pH monitoring system[a] because we found it reliable and minimally invasive for extended continuous gastric pH monitoring in dogs.[11] This system allows longer measurement periods than catheter-based pH probes.[5] Compared with dogs, a shorter vacuum application time (approximately 20 seconds) worked better for pH capsule placement in cats. In the 4 cats with pH capsules still in place at the time of second capsule application, the vacuum was applied for ≥25 seconds, and we believe a larger part of the gastric mucosa became lodged in the suction well of the capsule (Fig. 1) compared with what we observed in dogs.[11] Inclusion of the lamina muscularis may have added to the rigidity of the attachment. Attempts to remove the first capsule failed, and we left them in place. We were aware of a case of gastric perforation related to endoscopic removal of a Bravo™ capsule,[25,a] and it is possible that our attempts at removal were too conservative.

Soft feces has been associated with PO administered omeprazole treatment in humans and dogs,[4,5,26] but how suppression of gastric acid secretion predisposes patients to this adverse effect is not well understood.

We used fecal score cut-offs of 3 and 4 and found that the treatments did not differ with respect to feces consistency.

Histologic examination of gastric and duodenal biopsy samples was done to rule out occult gastrointestinal disease that could have interfered with parietal cell function or duodenal drug absorption. In all cats, the gastric mucosa was heavily colonized with *Helicobacter spp.*, but no evidence of gastritis was observed. In humans, the relationship between gastritis caused by *H. pylori* and gastric acid secretion is controversial, and normal acid secretion as well as hyper- and hypo-chlorhydria have been reported.[1] Although the severity of gastritis did not seem to be correlated with gastric acid secretion, omeprazole treatment resulted in higher gastric pH in human patients infected with *H. pylori* than in patients free of *H. pylori*.[27] This effect of omeprazole is believed to be present because of the neutralization of substances produced by *H. pylori*.[27] We believe this scenario to be unlikely in the cats of our study because *H. pylori* infection is extremely rare in cats[28] and evidence of gastritis was not detected in the present study. Given the overall high prevalence of gastric mucosal colonization with *Helicobacter spp.* without concurrent gastritis in cats,[28] we concluded that gastric histology results were typical of what is seen in cats. The principal goal of histologic examination was to rule out occult gastric disease, which could have affected gastric acid secretion, and small bowel disease,[29] which could have affected drug absorption. The relationship between gastric acid secretion and *Helicobacter spp.* colonization in cats requires further study.

A significant increase in intragastric pH between days 4 and 7 was only recorded after twice-daily omeprazole administration, which was similar to reports in humans in which multiple omeprazole doses were needed for optimal effect.[23,30] True drug efficacy might be greater after multiple doses than what we were able to document during the 96-hour study period. Considering the strong and long-lasting attachment of the capsule to the gastric mucosa in cats when using a vacuum time >25 seconds, it should be possible to study the efficacy of gastric acid suppressants for longer than 4 days.

We saw considerable individual variation in response to treatment with omeprazole and much less so with ranitidine. For example, 1 cat consistently had close to 100% acid suppression (e.g. percentage of time pH was ≥4 was 95% when treated with twice-daily omeprazole), whereas another had extremely poor acid suppression (percentage of time pH was ≥4 was 3% when treated with twice-daily omeprazole). These findings are similar to those observed in humans[23,31] and may be a consequence of genetic polymorphism in the hepatic cytochrome P-450 system involved in the metabolism of omeprazole, which is a well-established explanation for people who do not respond to gastric acid suppressants.[32] In fact, recent studies on the acid suppressant effects of proton pump inhibitors in humans include analysis of cytochrome 450 genes and report pH measurements based on results of genotyping (i.e. extensive, intermediate, and poor metabolizers).[33]

The washout periods used in the present study varied slightly among treatments subject to staff availability. However, we feel that the protocols used in our experiments precluded drug carryover effects. The minimum washout period of 7 days (n = 5) pertained to 3 examinations preceded by placebo and 2 preceded by ranitidine. The next shortest washout period was 9 days (n = 2), pertaining to 2 examinations preceded by once-daily omeprazole. A minimum of 1 week washout period was chosen because full restoration of gastric acid secretion was shown 7 days after long-term administration of ranitidine in cats[9] and 5 days after long-term administration of omeprazole in people.[34]

In conclusion, twice-daily administration of omeprazole granules appears to be the treatment of choice for cats with acid-related gastrointestinal disease. Ranitidine and once-daily omeprazole cannot be recommended as acid suppressants in cats.

Footnotes

Acknowledgments

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