Evaluation of the Effect of Orally Administered Acid Suppressants on Intragastric pH in Cats

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**Background:** Acid suppressant drugs are a mainstay of treatment for cats with gastrointestinal erosion and ulceration. However, clinical studies have not been performed to compare the efficacy of commonly PO administered acid suppressants in cats.

**Hypothesis/Objectives:** To compare the effect of PO administered famotidine, fractionated omeprazole tablet (fOT), and omeprazole reformulated paste (ORP) on intragastric pH in cats. We hypothesized that both omeprazole formulations would be superior to famotidine and placebo.

**Animals:** Six healthy adult DSH colony cats.

**Methods:** Utilizing a randomized, 4-way crossover design, cats received 0.88–1.26 mg/kg PO q12h fOT, ORP, famotidine, and placebo (lactose capsules). Intragastric pH monitoring was used to continuously record intragastric pH for 96 hours beginning on day 4 of treatment. Plasma omeprazole concentrations at steady state (day 7) were determined by high performance liquid chromatography (HPLC) with ultraviolet detection. Mean percentage time that intragastric pH was ≥3 and ≥4 were compared among groups using ANOVA with a posthoc Tukey-Kramer test (α = 0.05).

**Results:** The mean percentage time ± SD that intragastric pH was ≥3 was 68.4 ± 35.0% for fOT, 73.9 ± 23.2% for ORP, 42.8 ± 18.6% for famotidine, and 16.0 ± 14.2% for placebo. Mean ± SD plasma omeprazole concentrations were similar in cats receiving fOT compared to those receiving ORP and in a range associated with acid suppression reported in other studies.

**Conclusions and Clinical Importance:** These results suggest that both omeprazole formulations provide superior acid suppression in cats compared to famotidine or placebo. Fractionated enteric-coated OT is an effective acid suppressant despite disruption of the enteric coating.

**Key words:** Bravo monitoring; Famotidine; Feline; Omeprazole.

When the protective mechanisms of the stomach are compromised, the acidic and proteolytic environment can contribute to the development of gastroduodenal ulceration.1–3 Disorders that may disrupt the gastroduodenal mucosal barrier include both gastric and nongastric diseases including gastrointestinal neoplasia, liver failure, critical illness, drug toxicity, gastrointestinal infections (eg, *Helicobacter*) and inflammatory bowel disorders among others.2,4–7 Gastric ulceration and its sequelae can be severe.2,6–9 Thus, gastric acid suppressants including histamine-2 receptor antagonists (H2RA) and proton pump inhibitors (PPIs) are among the most widely prescribed medications for adjunctive treatment of diseases that disrupt the mucosal barrier and predispose cats to development of gastrointestinal erosion and ulceration. Proton pump inhibitors including omeprazole increase intragastric pH by covalently binding to parietal cell proton pumps (H+−K+−ATPase), which represent the final common target for acid secretion.10 This inhibition is potent, acting against basal and stimulated gastric acid production. Omeprazole is more effective at increasing intragastric pH than H2RAs in both humans11 and dogs12,14 and is widely used for the treatment of acid-related disorders in these species.

Several barriers prevent optimal dosing of commercially available omeprazole formulations in cats. These include proposed dosing requirements that are not practically obtained by manipulation of dosage forms intended for humans and the inclusion of substances in some omeprazole formulations that are potentially toxic to cats. For example, the omeprazole suspension approved for humans12 is not a good option because it...
In a randomized, open-label, 4-way crossover design, cats were administered placebo10 (250 mg lactose capsule PO q12h), famotidine11 (0.88–1.26 mg/kg PO q12h), fractionated omeprazole tablets (0.1T12; 0.88–1.26 mg/kg PO q12h) or omeprazole reformulated paste (ORP13; 0.88–1.26 mg/kg PO q12h) for 7 consecutive days followed by a minimum 10-day washout period. Cats were randomized to a treatment group using a random number generator. The goal of treatment was to achieve a dosage that approximated 1 mg/kg PO q12h in all treatment arms. The dosage of each drug was kept consistent among treatment arms for each cat (eg, cat 1 received 1.1 mg/kg PO q12h for all study drugs). Omeprazole paste was reformulated to a suspension at a concentration of 10 mg/ml by mixing an approved oral paste for horses (Gastrogard) in cod liver oil at a ratio of 1:39 and stored at a controlled cold temperature (7°C) protected from light. To be conservative, a beyond use date of 90 days was assigned to the refrigerated reformulated paste, which is within the US Pharmacopeial standard of 180 days for nonaqueous compounded oral liquids. Cats were medicated at 7:30 am and 5:30 pm daily. Each medication was followed by oral syringe administration of 3 ml of water and swallowing of the medication was witnessed. Cats were fed a maintenance diet14 30 minutes after medicating at 8:00 am and 6:00 pm daily. This time interval was selected to best mimic the feeding schedule of many client-owned cats. Cats had unlimited access to water during the pH monitoring period. Each medication when it occurred. Feces were graded from 1 to 7 by a standardized fecal scoring system. The authors’ knowledge, comparative studies investigating the clinical efficacy of PO administered omeprazole formulations and famotidine in cats are not available. Therefore, the purpose of this study was to examine the effect of PO administered fractionated omeprazole tablet, omeprazole reformulated paste and famotidine on intragastric pH in cats. On the basis of previous evidence in human and canine medicine, we hypothesized that both omeprazole formulations would be more efficacious in increasing feline intragastric pH than famotidine or placebo. A continuous analysis of the pharmacodynamics of omeprazole and famotidine on gastric pH in cats was obtained using a minimally invasive continuous intragastric pH monitoring device. In addition, we sought to compare the pharmacokinetics of the 2 omeprazole formulations at steady state.

Materials and Methods

Cats

The Institutional Animal Care and Use Committee (IACUC) at the University of Tennessee approved the protocol for this study (Approval #2193-0693). The subjects of this study were 7 healthy adult domestic shorthair cats from a research colony at the University of Tennessee (3 neutered females, 4 neutered males), aged 3–10 years (median, 5 years) and weighing 3.97–5.68 kg (median, 4.55 kg). Cats included in the study were deemed healthy on the basis of normal physical examination, normal CBC and biochemistry profile performed within 6 months of study entry. In addition, cats had no evidence of gastrointestinal disease and had normal PCV, as well as normal total serum protein, blood urea nitrogen and blood glucose concentrations and urinalysis results at study entry. To ensure inclusion of healthy cats and to comply with IACUC guidelines, cats were excluded from the study if they developed inappetence for >24 hours, lost >10% of their body weight, had gross evidence of disease on gastroesophagography during the study period or some combination of these. Four times per day, cats were allowed to roam in an enclosed room and were engaged in playful activities. The receivers remained in the middle of the room within 6 feet of the cats at all times to allow for continued data collection during free-roaming periods.

Placement of Intragastric pH Monitor

On the morning of day 4 of each treatment period, the morning meal was withheld and cats were anesthetized for gastroscopy-assisted placement of a Bravo pH capsule. Cats were premedicated with dexmedetomidine (0.005 mg/kg), ketamine (5 mg/kg) and butorphanol (0.4 mg/kg) IM. An IV catheter was placed and general anesthesia was induced with propofol to effect. Cats were maintained with sevoﬂurane in 100% oxygen after endotracheal tube placement. Peripheral catheters were placed under premedication to allow for induction drug administration and blood sampling. Gastroscopy was performed with cats in left lateral recumbency to aid in position and attachment of the pH capsule to the fundic mucosa, 2–5 cm distal to the lower esophageal sphincter. This location was kept consistent among treatment groups by utilizing the measurements on the insertion tube of the scope to measure the distance from the canine teeth to the lower esophageal sphincter (LES) and from the LES to the area of desired capsule placement. At initial endoscopy for each cat, the entire stomach and esophagus were evaluated for evidence of gross disease. Immediately before capsule placement, the capsule and 2 receivers for each cat (1 for the first 48 hours and 1 for the second 48 hours) were calibrated with commercial buffer solutions (pH 1.07 and 7.01) according to...
manufacturer’s instructions. The capsule, preassembled with a catheter delivery system, was introduced into the stomach transorally. Once the desired position of the capsule was verified, mucosal attachment of the pH capsule was achieved as previously reported according to the manufacturer’s instructions with some modifications. External vacuum suction was applied to the capsule delivery system to achieve a minimum of 510 mmHg for 15 seconds. This protocol was altered from the manufacturer recommendations of 30 seconds to allow for natural passage of the capsule in cats. The protocol was altered because of 1 of the author’s (MKT) experience that cats retain capsules for a longer period of time compared to dogs. After application of vacuum suction (Fig. 1A), a spring-loaded pin mechanism was initiated to engage suctioned mucosa within the capsule well. The vacuum source was turned off and the delivery system was withdrawn from the cat. Mucosal attachment of the capsule was confirmed by endoscopic visualization of secured mucosa within the well of the capsule (Fig. 1B). Capsules that remained adhered to the gastric mucosa from the previous treatment upon placement of a new capsule were either removed by a polypectomy snare or were allowed to slough off the gastric mucosa. Cats were reversed with atipamezole (0.05 mg/kg IM) after the procedure.

**pH Recordings**

Intragastric pH recordings were obtained telemetrically at 6-second sampling intervals for 96 hours (days 4–7 of treatment) after capsule placement. Data receivers were kept near the cage or on the cage door of all cats during the data acquisition phase. After 48 hours of pH data acquisition (the maximal amount of data held by the receiver), pH data was uploaded from the first receiver to the computer using manufacturer software (Polygram Net®). The percentage of time that intragastric pH was ≥ 6.5 was calculated by the computer software. The second receiver previously calibrated to the existing capsule was either removed by a polypectomy snare or were allowed to slough off the gastric mucosa. Cats were reversed with atipamezole (0.05 mg/kg IM) after the procedure.

**Statistical Analysis**

Intragastric pH measurements, fecal scores, and percentage food consumption were compared by treatment. For pH, the effects of day of treatment and time of treatment and feeding also were assessed. Data were analyzed using mixed effects analysis of variance (ANOVA) to model the 4-way crossover design and account for the random effect of subjects nested within treatment sequence. When repeated measurements occurred, a first order autoregressive covariance structure was specified for the residual matrix. Covariance parameters were estimated using a restricted maximum likelihood estimation method, and denominator degrees of freedom for the tests of fixed effects were estimated using computer software. A 1-compartment model with first order input and elimination and no lag time, according to the following equation was used:

\[
C(t) = \frac{D_{po} \times F \times K_{e}}{V \times (K_{01} - K_{10}) \times [e^{-K_{10} \times t} - e^{-K_{01} \times t}]},
\]

where \( C \) is plasma concentration at time \( t \), \( D_{po} \) is oral dose, \( F \) is bioavailability (unknown in this study), \( V \) is volume of distribution divided by bioavailability, \( K_{e} \) is the absorption rate constant, and \( K_{10} \) is the elimination rate constant. Plasma concentrations were weighted by the reciprocal of the predicted value squared to obtain the best fit. The best fit model was chosen based on visual inspection of the data, residual plots, and Akaike’s Information Criterion (AIC). Values for \( C_{MAX} \) and \( T_{MAX} \) were taken directly from the data.

**Sample Collection and Pharmacokinetic Analysis**

Blood samples were obtained from cats receiving fOT or ORP on day 7 of treatment (steady state). Blood (1 ml) was collected from a peripheral catheter into heparinized tubes 0.25, 0.5, 1, 2, 4, 6, and 8 hours after administration of the morning medication. Blood samples were centrifuged at 250 x g for 10 minutes. Plasma was transferred to a cryovial and stored at −80°C until analyzed. All plasma samples were analyzed for omeprazole concentration within 3 months of collection using HPLC with ultraviolet detection using a previously published method with partial validation to account for feline plasma. The limit of quantification was 0.01 μg/ml. A zero value was assigned to all measurements determined to be below the limit of quantification. Pharmacokinetic parameter estimates for each omeprazole formulation were estimated using computer software. A 1-compartment model with first order input and elimination and no lag time, according to the following equation was used:

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puted using the Kenward-Roger method. F-tests were obtained for all main effects and for interactions when multifactor models were used. The Shapiro-Wilk test was used to test the ANOVA assumption of normally distributed errors, and the Levene's F test was used to test the assumption of homogeneity of variance. When necessary, data were logarithmically (normal) transformed. Both assumptions were met with transformed data. To minimize the probability of type I error, a Bonferroni adjusted alpha of 0.003 was used to evaluate the ANOVA results. When a significant treatment effect was observed, a posthoc Tukey-Kramer test was performed to determine which groups were significantly different from each other (protected $\alpha = 0.05$). No significant period or sequence effects were found for any dependent variable. A t-test and Mann-Whitney Rank Sum test were used to analyze parametric and nonparametric pharmacokinetic data, respectively. For pharmacokinetic analyses, a $P$ value of $<0.05$ was considered significant. Commercially available statistical software was used to perform all data analysis and to produce all descriptive statistics.9

Results

Use of the Bravo pH Monitoring System in Cats

All 24 Bravo pH capsules were successfully attached to the fundic gastric mucosa. Total procedure times for gastroscopy-assisted capsule attachment ranged from 5 to 10 minutes. On 12 of 24 occasions, the previously placed Bravo pH capsule remained in place and an additional 5–15 minutes of procedure time was required to remove the attached capsule. Because of difficulty removing the capsule and concern for perforation associated with removal of firmly adhered capsules, 5 capsules were left adhered followed by placement of a new capsule in the area immediately adjacent to the previous capsule. On 3 occasions, the capsule dislodged during the washout period and passed uneventfully in the feces. In contrast to experience with dogs, no capsules detached prematurely during the study period. Because of receiver malfunction, data was not captured for 86 hours of a total of 2304 hours, although the Bravo pH capsules remained appropriately adhered. This may have been the result of lost signal because the receivers could not be placed directly on the cats because of the size of the receiver and patient. The majority of the lost data occurred in the evening when the receivers were not monitored as frequently. On 4 occasions, the receiver continued to read from the previously placed capsule (at least 14 days earlier). Data from 1 cat were excluded from study results after the onset of progressive inappetence, weight loss, and suspicion of eosinophilic gastroenteritis. Additional information on this cat is published elsewhere.7

Intragastric pH Recordings

The mean percentage time intragastric pH was $\geq 3$ and $\geq 4$ is considered the ideal baseline for encouraging healing of gastrointestinal disease as determined by meta-analysis studies in humans.11 Thus, mean percentage time intragastric pH was $\geq 3$ and $\geq 4$ was used for comparative analyses of treatments. The mean percentage time $\pm$ SD the intragastric pH was $\geq 3$ and $\geq 4$ were $68.4 \pm 35.0\%$ and $57.8 \pm 37.1\%$ for iOT, $73.9 \pm 23.2\%$ and $55.7 \pm 25.3\%$ for ORP, $42.8 \pm 18.6\%$ and $22.4 \pm 14.7\%$ for famotidine, and $16.0 \pm 14.2\%$ and $9.6 \pm 10.1\%$ for placebo, respectively. For the mean percentage time intragastric pH was $\geq 3$ and $\geq 4$ over the 4-day study period, both omeprazole formulations significantly increased intragastric pH compared to famotidine or placebo ($P < .0001$; Fig 2). Differences also were observed in the distribution of intragastric pH over pH categories 1–8 when comparing omeprazole formulations to famotidine and placebo (Fig 3). No differences were observed when comparing omeprazole formulations to each other in any category. As in dogs, intragastric pH fluctuated widely across all pH categories in cats receiving all treatments, but both omeprazole formulations resulted in more time intragastric pH fell between pH categories 3–4 and 7–8. The mean percentage time intragastric pH was $\geq 3$ and $\geq 4$ was significantly higher in cats receiving famotidine compared to placebo ($P < .0001$). The mean percentage time intragastric pH was $\geq 3$ and $\geq 4$ also was used to determine if there was an effect on the order of treatment, day of treatment, and time of day (morning or evening treatment) on intragastric pH between or within certain groups. For all cats, on the order of treatment did not significantly affect the percentage time intragastric pH was $\geq 3$ and $\geq 4$ over the 96-hour recording period ($P = .8807$). Similarly, no significant differences were identified for the mean percentage time intragastric pH was $\geq 3$ and $\geq 4$ when comparing days 4 through 7 of treatment within each group ($P = .3043$). There were no significant differences in the percentage time intragastric pH was $\geq 3$ and $\geq 4$ between the 1st and 2nd 2-hour periods within each treatment group ($P = .1388$). In addition, a buffering effect of food on intragastric pH was not identified in the placebo control group ($P = .7851$). The mean pH $\pm$ SD for cats in the placebo group over the 96-hour period was 2.3 $\pm$ 0.4. Adverse Effects of Treatment

Vomiting was noted in 2 cats with a total occurrence of 6 episodes of emesis. None of these episodes occurred immediately after medicating, and no medications were observed in the vomitus. There were 3 episodes of vomiting each in the placebo and ORP groups. There was no significant association with treatment received and inappetence, consistency of stool, number of defecations with a fecal score of $\geq 4$, or changes in attitude. There were 8 episodes of inappetence in the famotidine group, 16 episodes in the iOT group, 11 episodes in the ORP, and 7 episodes for the placebo group. The mean $\pm$ SD fecal score was 3.1 $\pm$ 0.8 for the famotidine group, 2.6 $\pm$ 0.5 for the iOT group, 2.7 $\pm$ 0.9 for the ORP group, and 2.9 $\pm$ 0.1 for the placebo group. There were 9 episodes of fecal scores $\geq 4$ in the famotidine group and 6 episodes each in the iOT and ORP groups. There were
6 days of defecations with a fecal score $\geq 4$ in the famotidine group, 3 days in the fOT group and 5 days in the ORP group. No defecations with a fecal score $\geq 4$ occurred in the placebo group.

**Pharmacokinetic Analysis**

Plasma concentration (mean $\pm$ SD) data were available for 6 cats receiving ORP and 5 cats receiving fOT (Fig. 4). In 2 cats that received fOT, a full set of data was not obtained and thus values from these cats were omitted from analysis of pharmacokinetic parameters. In 1 of these 2 cats, concentration data were only detectable for 3 time points which precluded fitting to the compartmental model; however, these 3 time points were included in graphical representation of the data (Fig. 4). Plasma concentrations were detectable in all 6 cats receiving ORP and in 2 of 5 cats receiving fOT at 15 minutes postmedication. Plasma concentrations were undetectable in 5 of 6 cats receiving ORP.
and in 3 of 5 cats receiving fOT by 6 hours postmedi-
cation. Pharmacokinetic parameter estimates are listed
in Table 1. A significant difference was found when
comparing T MAX in cats receiving ORP compared to
fOT (P = .03), where the median T MAX for ORP was
0.5 hours versus 2 hours for fOT. No other parameters
were found to be significantly different.

Discussion

Gastric erosion and ulceration are common sequelae
to a wide range of gastric and nongastric acid-related
disorders in cats. For this reason, acid suppressants
are among the most widely prescribed medications for
cats. Generic tablets containing omeprazole (OT) or
famotidine are commonly prescribed acid suppressants.
However, to the authors’ knowledge, no clinical stud-
ies have been performed in cats to determine the effi-
cacy of these different acid suppressants. This study
was undertaken to compare the efficacy of PO admin-
istered famotidine to omeprazole formulations in cats
using the Bravo pH monitoring system. The mean per-
centage time gastric pH is ≥3 and ≥4 is considered the
ideal baseline for encouraging healing of gastrointesti-
nal disease as determined by meta-analysis studies of
humans. Therefore, the mean percentage of time the
intragastric pH was ≥3 and ≥4 was used for purposes
of comparative analyses among treatment arms. Our
results demonstrate that omeprazole formulations pro-
vide superior acid suppression compared to famotidine
and placebo. Moreover, only omeprazole formulations
administered to cats approached goals established
for treatment of people with gastroduodenal ulcers
and gastroesophageal reflux disease, demonstrated
to be optimal at an intragastric pH of ≥3.0 and ≥4.0
for approximately 75% and 67% of the day, respectively.

Delayed-release OT contains a protective enteric
coating on its surface to prevent premature gastric
degradation. Omeprazole tablets are only widely avail-
able in sizes of 20 mg and larger. A major limitation
in appropriately dosing cats is their small body size,
resulting in a much smaller total dose of medication
needed than provided as a nondivided tablet. Thus,
lacking other practical alternatives, veterinary prac-
titioners often divide these tablets for optimal dosing in
cats. The efficacy of the tablets after damage to their
enteric coating is unknown. To evaluate the efficacy
of omeprazole tablets after disruption to their protective
coating, we directly compared their pharmacokinetics
at steady state (day 7 of treatment) and their pharma-
codynamics (days 4–7 of treatment) using mean per-
centage time intragastric pH was ≥3 and ≥4 over the 4-
day study period to an omeprazole reformulated paste
(ORP) recently shown to be highly efficacious in
dogs. No significant differences were found between
fOT and ORP when comparing mean percentage time
intragastric pH was ≥3 and ≥4 over the 4-day study
period. Moreover, there were no differences in any of
8 pH categories when comparing the 2 omeprazole for-
mulations. Mean ± SD plasma omeprazole concentra-
tions of both formulations were similar. Evaluation of
the pharmacokinetic parameter estimates indicated
that time to peak omeprazole concentration (T MAX)
occurred earlier in cats receiving ORP, perhaps
because fOT required more time for tablet dissolution.

Table 1. Pharmacokinetic variable estimates (median
and range) for cats receiving omeprazole reformulated
paste (ORP) or fractionated omeprazole tablet (fOT)
on day 7 of treatment.

| Parameter | ORP (n = 6) | fOT (n = 4) | P value |
|-----------|------------|------------|---------|
|          | Median     | Range      | Median  | Range      |         |
| AUC (µg/hr/mL) | 0.46 | 0.21–0.94 | 0.57 | 0.33–1.4 | .394 |
| Cmax (µg/mL)   | 0.35 | 0.05–0.78 | 0.11 | 0.09–0.85 | .705 |
| TMAX (hr)     | 0.5  | 0.25–1.0  | 2.0  | 0.5–4.0   | .03   |
| Elim        | 0.9  | 0.07–0.25 | 0.83 | 0.66–1.75 | .806 |
| T1/2 (hr)    |       |           |       |           |       |
Similar to previous studies in dogs,9,13,14 famotidine was found to be more efficacious than placebo in cats but was inferior to omeprazole in suppression of acid production.8 Thus, the authors recommend that omeprazole be administered to cats with documented acid-related disorders.

The optimal omeprazole dosage in small animal patients has not been established.3,24,25 However, studies in dogs in which lower dosages of omeprazole (0.7–1.0 mg/patient q24h) were used resulted in suboptimal performance, did not meet goals established for people with acid-related disorders or both.9,13,14,23 The chosen dosage and frequency for omeprazole in this study (approximately, 1 mg/kg PO q12h) were based on those recently demonstrated to provide superior acid suppression in dogs.2,14 Future work will be necessary to determine if this is the appropriate dosage for cats at risk for or with documented acid-related disorders.

Previous studies performed on cats evaluated the efficacy of acid suppressants by measurement of the pH of gastric secretions obtained from a surgically placed gastric fistula.3,23 Artificial disruption of normal gastric anatomy and physiology by placement of a gastric fistula and pharmacologic stimulation of gastric acid secretion may not accurately reflect intragastric pH in the clinical patient. The Bravo pH monitoring system was selected in this study, because wireless continuous pH monitoring systems are being used with increasing frequency in patients with gastric disease and displaced pH probes (ie, less impairment of normal activities), and provide reliable results.26,27 These monitoring systems have been shown to be more physiologic and more accurate than aspiration of gastric secretions, more accurate than aspiration of gastric secretions, more accurate than aspiration of gastric secretions, and more accurate than aspiration of gastric secretions, and more accurate than aspiration of gastric secretions, and more accurate than aspiration of gastric secretions, and more accurate than aspiration of gastric secretions.

In conclusion, these results suggest that both omeprazole formulations provide superior acid suppression in cats compared to famotidine or placebo. The fractionated enteric-coated omeprazole tablet remains efficacious despite disruption of its enteric coating, allowing for more convenient, titratable dosing in cats. In addition, the Bravo pH monitoring system can be safely used in healthy cats for continuous intragastric pH monitoring, but, the safety of its use in cats with GI disease needs to be evaluated.
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Conflict of Interest: Authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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