

Effects of ranitidine, famotidine, pantoprazole, and omeprazole on intragastric pH in dogs

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Objective—To identify the normal gastric acid secretion profile in dogs and determine the degree of gastric acid suppression associated with 4 gastric acid suppressants.

Animals—12 healthy Beagles.

Procedure—Intragastric pH was measured continuously for 24-hour periods with a digital recording system placed via a gastrostomy tube. Baseline measurements were obtained when food was withheld and when dogs were fed a standard diet. Dogs were then treated with ranitidine (2 mg/kg, IV, q 12 h), famotidine (0.5 mg/kg, IV, q 12 h), pantoprazole (1 mg/kg, IV, q 24 h), omeprazole (1 mg/kg, PO, q 24 h), or saline solution for 7 days; intragastric pH was recorded on days 0, 2, and 6. Subsequently, the effects of administering famotidine (0.5 mg/kg, IV, q 8 h; 6 dogs) and omeprazole as a suspension (1 mg/kg, PO, q 12 h; 6 dogs) were evaluated. Median 24-hour intragastric pH, percentage of time pH was ≥ 3 , and percentage of time pH was ≥ 4 were determined.

Results—Median pH, percentage of time pH was ≥ 3 , and percentage of time pH was ≥ 4 were all significantly higher when food was withheld than when dogs were fed. Famotidine, pantoprazole, and omeprazole significantly suppressed gastric acid secretion, compared with saline solution, as determined on the basis of median 24-hour pH and percentages of time pH was ≥ 3 or ≥ 4 . However, ranitidine did not. Omeprazole suspension suppressed gastric acid secretion.

Conclusions and Clinical Relevance—Results suggest that in healthy dogs, famotidine, pantoprazole, and omeprazole significantly suppress gastric acid secretion. Twice daily administration of a suspension of omeprazole, was the only regimen tested that approached the potential therapeutic efficacy for acid-related disease when assessed by criteria used for human patients. (*Am J Vet Res* 2005;66:425–431)

A large body of information exists regarding gastric acid secretion and its suppression in humans and dogs,¹⁻⁷ and several drugs have been shown in experimental studies to have an effect on intragastric pH in dogs. However, previous studies involving dogs were

most often performed as an adjunct to development of gastric acid suppressants for use in humans. Thus, these studies were not specifically aimed at determining the extent or duration of gastric acid suppression in dogs in clinically relevant settings. Earlier studies, for instance, measured effects in dogs after gastric acid secretion was altered pharmacologically with pentagastrin or histamine,³⁻⁷ were focused on determining toxic effects following administration of extremely high dosages,^{4,5} or involved measuring intragastric pH for short periods or only intermittently.^{1-3,7} As a result, little is known about the effects in dogs of commonly used gastric acid suppressants administered as recommended in the veterinary literature.

In addition, despite the common use of gastric acid suppressants in dogs, to our knowledge, there are no published comparative studies specifically investigating the efficacy of gastric acid suppression in the veterinary literature. In humans, healing of gastric and duodenal ulcers and erosive esophagitis is highly correlated with the degree of gastric acid suppression.⁸ For people with duodenal ulcers, for instance, optimal treatment involves maintaining an intragastric pH ≥ 3 for 18 to 20 hours a day (ie, approx 75% of the day) and little benefit is associated with more extensive gastric acid suppression.⁹ In people with gastroesophageal reflux disease, intragastric pH should be ≥ 4 for 16 to 22 hours a day.¹⁰ A critical intragastric pH threshold of 4 is also recommended for prevention of gastrointestinal tract ulcers in critically ill patients because pH values > 4 inactivate pepsin and inhibit fibrinolysis.¹¹ Finally, an intragastric pH > 6 is necessary to achieve hemostasis with acute gastrointestinal tract bleeding, as pH values > 6 allow adequate platelet aggregation and prevent dissolution of blood clots.¹¹

The optimal degree of gastric acid suppression necessary for treating acid-related diseases in dogs has not been established, and critical intragastric pH thresholds in dogs may differ from those established for humans because of differences in gastric physiology. Regardless, it seems likely that the degree and duration of gastric acid suppression will correlate with ulcer healing in dogs as it has in humans.⁹ The purposes of the study reported here were to identify the normal gastric acid secretion profile in healthy dogs that were fed and from which food had been withheld and to determine the degree and duration of gastric acid suppression associated with 4 gastric acid suppressants (2 histamine₂ [H₂] receptor antagonists and 2 proton pump inhibitors) commonly prescribed in dogs.

Materials and Methods

Dogs—Twelve purpose-bred sexually intact Beagles (5 males and 7 females) were used in the study. Dogs ranged

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from 7 months to 5 years old (median, 14 months; mean, 23 months) and weighed between 7.5 and 12.7 kg (median, 9.8 kg; mean, 9.9 kg). All dogs were determined to be healthy on the basis of results of a general physical examination, CBC, and serum biochemical profile. In all dogs, a **percutaneous, endoscopically placed gastrostomy (PEG) tube** was inserted in the gastric fundus at least 2 weeks prior to the start of the study. Multiple biopsy specimens were obtained from the fundus of the stomach at the time of PEG tube placement and submitted for *Helicobacter* screening. All dogs were considered to be negative for *Helicobacter* spp on the basis of results of a urea slant test, routine bacterial culture, and a generic polymerase chain reaction assay. General physical health of the dogs was subsequently monitored by means of weekly physical examinations, at which time body weight was also recorded.

Measurement of intragastric pH—Intragastric pH was recorded continuously with a digital recording system; dogs were fully ambulatory while intragastric pH was recorded. In brief, intragastric pH was measured with a single-channel, internally referenced glass pH probe^a attached to a portable data recorder.^b Before and after each recording session, the electrode was calibrated with commercial buffer solutions^c of pH 1.7 and pH 7 at 21°C; a drift of 0.1 pH units was tolerated. Following calibration, the probe was passed into the stomach through the PEG tube and secured with adhesive tape. The probe extended 5 to 7 cm beyond the PEG tube into the fundus of the stomach. Prior to the study, appropriate probe positioning was confirmed in 2 dogs by means of fluoroscopy, and this same positioning was used for all dogs in the study. During recording sessions, intragastric pH was recorded every 4 seconds by the data recorder. Following a recording session, pH data were downloaded to a data file^d and stored for later analysis.

Determination of normal gastric acid secretion profile—In all dogs, the normal gastric acid secretion profile was determined while food was withheld and while dogs were fed. To determine gastric acid secretion while food was withheld, dogs were fed at 8:00 PM the night prior to a recording session. Food was then withheld overnight, and beginning at 9:00 AM the next morning, intragastric pH was measured continuously for 24 hours. Food was withheld during the entire 24-hour recording session.

One week later, gastric acid secretion was measured while dogs were fed. Briefly, intragastric pH was measured continuously for 24 hours, beginning at 9:00 AM. Dogs were fed three fourths of a cup of kibble^e at 10:00 AM, 3 dog treats^f at 3:00 PM, and three fourths of a cup of kibble at 8:00 PM and again at 8:00 AM the following morning. Probes were removed at 9:00 AM. Water was available ad libitum during recording sessions.

Effects of H₂ receptor antagonists and proton pump inhibitors—Following determination of the normal gastric acid secretion profile, a randomized controlled trial was performed to determine the effects of 2 H₂ receptor antagonists (ranitidine and famotidine) and 2 proton pump inhibitors (pantoprazole and omeprazole). The study was constructed as a randomized Latin-square design with repeated measures over days.¹² The feeding schedule used during determination of the normal gastric acid secretion profile was maintained throughout this portion of the study. Dogs were treated with ranitidine^g (2 mg/kg, IV, q 12 h), famotidine^h (0.5 mg/kg, IV, q 12 h), pantoprazoleⁱ (1 mg/kg, IV, q 24 h), omeprazole^j (approx 1 mg/kg, PO, q 24 h), or saline (0.9% NaCl) solution (3 mL, IV, q 12 h). Drugs were administered for 1 week, and intragastric pH was measured for 24 hours immediately prior to the initiation of each treatment and on days 2 and 6 of each treatment period. All dogs received all 5 treatments. In each dog, treatments were administered in random order

with 1 week between treatments; randomization schedules were developed with a random number generator.¹³ Any complications or adverse effects identified during treatment periods were recorded.

Dosages of ranitidine, famotidine, and omeprazole were selected on the basis of published recommendations.¹⁴⁻¹⁶ The highest recommended dosages of ranitidine and famotidine were selected in an attempt to maximally inhibit gastric acid secretion. A 12-hour dosing frequency was selected, as we believed that compliance with more frequent administration guidelines tends to be poor in clinical practice. For administration of omeprazole, 10-mg tablets were administered as necessary to approximate the target dosage; the actual dosage administered ranged from 0.8 to 1.3 mg/kg. The dosage of pantoprazole was selected on the basis of information generated in dogs during development of the drug for human use.^{4,17,k} Pantoprazole solution was prepared by injecting 10 mL of saline solution into the vial containing the dry powder; concentration of the final solution was 4 mg/mL. Pantoprazole was used within 4 hours after preparation. All injectable drugs were prepared daily by technical staff unrelated to the project. Syringes were labeled Nos. 1 to 6 to identify the recipients. Drug volumes were all made up to 3 mL by the addition of saline solution. All drugs were administered at 9:00 AM and 9:00 PM during treatment periods; injectable drugs and saline solution were administered over 15 minutes. Researchers administering drugs and downloading pH determinations were blinded to the drugs delivered. Omeprazole was excluded from the blinding as it was administered orally as a single 10-mg tablet. The study was unmasked on completion of data collection.

Effects of dosing frequency—In 6 dogs, a study was performed to determine whether increasing the frequency of famotidine administration would have a significant effect on gastric acid secretion. In these dogs, famotidine was administered at a dosage of 0.5 mg/kg, IV, every 8 hours for 1 week. Intragastric pH was measured for 24 hours on days 2 and 6 of the treatment period.

In 6 dogs, a study was performed to determine whether increasing the frequency of omeprazole administration, with omeprazole formulated into a suspension, would have a significant effect on gastric acid secretion. Omeprazole suspension (2 mg of omeprazole/mL of 8.4% sodium bicarbonate) was prepared as described¹⁸ and administered at a dosage of 1 mg/kg every 12 hours for 1 week. The omeprazole suspension was administered as a bolus through the PEG tube; the tube was flushed with 10 mL of water following drug administration. Intragastric pH was measured for 24 hours on days 2 and 6 of the treatment period.

Statistical analyses—For each 24-hour recording of intragastric pH, median pH, percentage of time intragastric pH was ≥ 3 , and percentage of time intragastric pH was ≥ 4 were determined. Paired *t* tests were used to compare values obtained for normal gastric acid secretion when dogs were fed with values obtained when food was withheld.

For evaluation of the effects of ranitidine, famotidine, pantoprazole, and omeprazole, ANOVA for repeated measures was performed with main effects being treatment and day and controlling for the effects of dog, drug carryover, and week. The Dunnett test was used to compare, for each day, values obtained for each of the 4 drugs with values obtained during administration of saline solution. The Tukey test was used to compare, for each drug, values obtained each day and, for each day, values obtained for the 4 drugs.

For evaluation of the effect of dosing frequency of famotidine on gastric acid secretion, ANOVA was used to analyze data obtained. Post hoc pairwise *t* tests were performed to determine significant differences.

For all analyses, assumptions of normality were tested by means of the Shapiro-Wilk test; equality of variance assumptions were assessed by plotting residuals against explanatory variables and against the predicted value. Logarithmic transformations were performed as necessary. All statistical analyses were performed with standard software.¹⁹ Values of $P \leq 0.05$ were considered significant.

Results

Normal gastric acid secretion profile—Median 24-hour intragastric pH when food was withheld from the dogs (mean, 4.44; 95% confidence interval (CI), 3.33 to 5.92) was significantly ($P < 0.001$) higher than median 24-hour intragastric pH when dogs were fed (1.30; 95% CI, 1.11 to 1.52). Percentage of time that intragastric pH was ≥ 3 was significantly ($P < 0.001$) higher when food was withheld (mean, 66.0%; 95% CI, 52.4% to 83.0%) than when dogs were fed (13.3%; 95% CI, 8.9% to 19.8%). Similarly, percentage of time that intragastric pH was ≥ 4 was significantly ($P < 0.001$) higher when food was withheld (63.9%; 95% CI, 47.4% to 80.4%) than when dogs were fed (12.8%; 95% CI, 7.3% to 18.3%).

Effects of ranitidine, famotidine, pantoprazole, and omeprazole—One dog developed a gastrointestinal tract disturbance and vomited several times during the week that saline solution was administered. Therefore, values for saline solution were based on data for only 11 dogs.

Values for median 24-hour intragastric pH, percentage of time intragastric pH was ≥ 3 , and percentage of time intragastric pH was ≥ 4 obtained during the time that saline solution was administered (days 0, 2, and 6) were compared with each other and with values obtained prior to administration of each of the 4 gastric acid suppressants (day 0). No significant differences were detected.

Values for median 24-hour intragastric pH on days 2 and 6 were significantly higher when dogs were given famotidine, pantoprazole, or omeprazole than when they were given saline solution (Table 1). However, values obtained on days 2 and 6 when dogs were given ranitidine were not significantly different from values obtained when dogs were given saline solution.

On days 2 and 6, percentage of time that intragastric pH was ≥ 3 was significantly greater when dogs were given famotidine, pantoprazole, or omeprazole than when dogs were given saline solution (Table 2). However, percentage of time that intragastric pH was ≥ 3 when dogs were given ranitidine was not significantly different from the percentage when dogs were given saline solution.

When dogs were given omeprazole, percentage of time that intragastric pH was ≥ 4 was significantly greater on day 2 than when dogs were given saline solution. On day 6, however, percentage of time that intragastric pH was ≥ 4 was significantly greater when dogs were given famotidine, pantoprazole, or omeprazole than when they were given saline solution (Table 3). When plotting the results of all 5 drug regimens over a 24-hour period, gastric pH followed a similar pattern; however, the differences in the percentages of time that the pH was ≥ 3 or ≥ 4 among drugs were apparent (Figures 1 and 2).

Comparison of the effects of the 4 drugs revealed that on day 2, median 24-hour intragastric pH when dogs were given omeprazole was significantly higher than median pH when dogs were given ranitidine, whereas on day 6, values for median pH when dogs were given famotidine, pantoprazole, or omeprazole were significantly higher than values obtained when dogs were given ranitidine. Similarly, on day 2, per-

Table 1—Median 24-hour intragastric pH in 12 healthy dogs treated with ranitidine (2 mg/kg, IV, q 12 h), famotidine (0.5 mg/kg, IV, q 12 h), pantoprazole (1 mg/kg, IV, q 24 h), omeprazole (1 mg/kg, PO, q 24 h), or saline solution (0.9% NaCl) for 7 days.

Measurement day	Saline solution	Ranitidine	Famotidine	Pantoprazole	Omeprazole
Day 0	1.97 (1.54–2.52)	1.61 (1.27–2.03)	1.68 (1.32–2.12)	1.78 (1.41–2.26)	1.52 (1.20–1.92)
Day 2	1.78 (1.39–2.28)	2.53 (2.00–3.20)	2.83* (2.23–3.59)	3.11* (2.45–3.93)	3.86*† (3.05–4.89)
Day 6	1.67 (1.31–2.14)	2.05 (1.62–2.60)	3.68*† (2.91–4.66)	3.49*† (2.76–4.42)	4.09*† (3.23–5.17)

Data are given as mean (95% confidence interval).
*Significantly ($P < 0.05$) different from value obtained when saline solution was administered. †Significantly ($P < 0.05$) different from value obtained when ranitidine was administered.

Table 2—Mean percentage of time intragastric pH was ≥ 3 in 12 healthy dogs treated with ranitidine, famotidine, pantoprazole, omeprazole, or saline solution for 7 days.

Measurement day	Saline solution	Ranitidine	Famotidine	Pantoprazole	Omeprazole
Day 0	36.4 (25.9–46.9)	27.7 (17.6–37.8)	27.8 (17.7–37.9)	31.6 (21.5–41.7)	26.2 (16.2–36.3)
Day 2	33.3 (22.7–43.8)	44.6 (34.5–54.7)	48.9* (38.8–59.0)	54.2* (44.1–64.3)	66.9*†† (56.8–77.0)
Day 6	29.1 (18.6–39.6)	37.2 (27.2–47.3)	60.1*† (50.0–70.2)	59.1*† (49.0–69.2)	70.2*† (60.1–80.2)

Data are given as mean percentage (95% confidence interval).
†Significantly ($P < 0.05$) different from value obtained when famotidine was administered.
See Table 1 for remainder of key.

Table 3—Mean percentage of time intragastric pH was ≥ 4 in 12 healthy dogs treated with ranitidine, famotidine, pantoprazole, omeprazole, or saline solution for 7 days.

Measurement day	Saline solution	Ranitidine	Famotidine	Pantoprazole	Omeprazole
Day 0	20.7 (14.0–30.7)	16.5 (11.4–24.1)	14.8 (10.2–21.6)	18.8 (12.9–27.4)	13.1 (9.0–19.1)
Day 2	22.6 (15.3–33.4)	26.8 (18.4–39.0)	30.5 (20.9–44.5)	34.7 (23.9–50.6)	44.9* (30.9–65.4)
Day 6	17.2 (11.6–25.4)	25.3 (17.4–36.9)	48.4* (33.2–70.5)	40.9* (28.1–59.6)	52.3*† (35.9–76.2)

Data are given as mean percentage (95% confidence interval).
See Table 1 for key.

centage of time intragastric pH was ≥ 3 was significantly higher when dogs were given omeprazole than when dogs were given ranitidine, and on day 6, percentage of time intragastric pH was ≥ 3 was significantly higher when dogs were given famotidine, pantoprazole, or omeprazole than when dogs were given ranitidine. Finally, on day 6, percentage of time intragastric pH was ≥ 4 was significantly higher when dogs were given omeprazole than when dogs were given ranitidine.

Significant drug carryover effects were identified when evaluating median 24-hour intragastric pH and percentage of time intragastric pH was ≥ 3 . This implied that potential drug interactions were evident, such that measured drug effects on intragastric pH were significantly dependent on the order in which drugs were administered. Famotidine and pantoprazole had more effects on subsequent measures than did ranitidine. These drug carryover effects were controlled for in study design and statistical analyses.

Effects of dosing frequency—No significant differences in median 24-hour intragastric pH, percentage of time intragastric pH was ≥ 3 , and percentage of time intragastric pH was ≥ 4 were found when famotidine was administered every 8 hours rather than every 12 hours.

Mean values for median 24-hour intragastric pH on days 2 and 6 when dogs were given omeprazole suspension were 4.7 (95% CI, 4.0 to 5.6) and 4.9 (95% CI, 4.1 to 5.8), respectively. Mean percentages of time intragastric pH was ≥ 3 were 90.9% (95% CI, 80.5% to 101.2%) on day 2 and 78.4% (95% CI, 68.1% to 88.8%) on day 6. Mean percentages of time that intragastric pH was ≥ 4 were 78.3% (95% CI, 63.8% to 92.8%) on day 2 and 70.7% (95% CI, 56.2% to 85.3%) on day 6. Although none of the dogs vomited on days that intragastric pH was recorded, vomiting (4 dogs) and diarrhea (4 dogs) were seen at various times after administration of the omeprazole-sodium bicarbonate suspension.

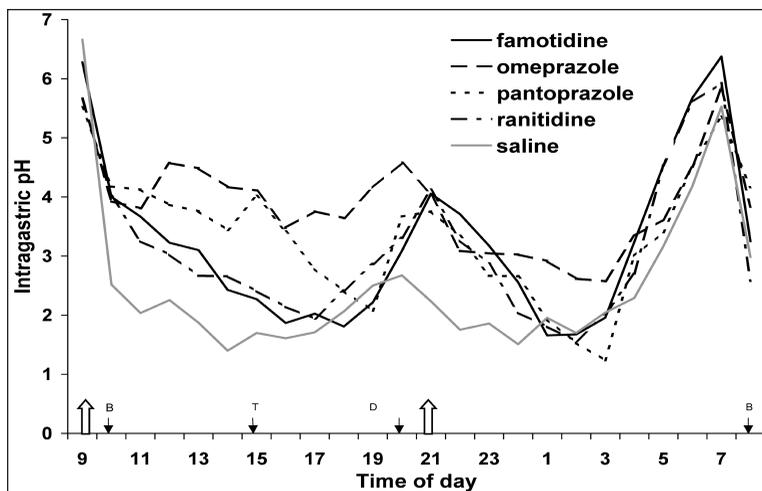


Figure 1—Median intragastric pH in 12 healthy dogs treated with ranitidine (2 mg/kg, IV, q 12 h), famotidine (0.5 mg/kg, IV, q 12 h), pantoprazole (1 mg/kg, IV, q 24 h), omeprazole (1 mg/kg, PO, q 24 h), or saline solution (0.9% NaCl) for 2 days. Drugs were administered at 9:00 AM and 9:00 PM (open arrows). Dogs were fed three fourths of a cup of kibble at 10:00 AM on the day of recording and 8:00 AM the following morning (B), 3 treats at 3:00 PM (T), and three fourths of a cup of kibble at 8:00 PM (D).

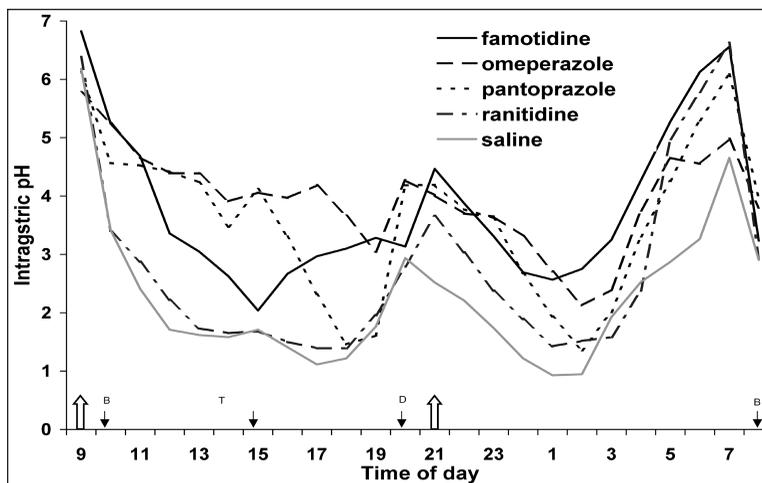


Figure 2—Median intragastric pH in 12 healthy dogs treated with ranitidine, famotidine, pantoprazole, omeprazole, or saline solution for 6 days. See Figure 1 for key.

Discussion

Previous studies^{1,2} have shown that the gastric acid secretion profile in Beagles is variable. For this reason, we elected to measure intragastric pH continuously for a 24-hour period, as we believed that this would provide the best measure of the fluctuations in intragastric pH.²⁰

One important limitation of the present study was that intragastric pH, rather than gastric acid secretion, was measured. Intragastric pH relates closely, but not exactly, to intragastric hydrogen ion concentration²¹ but does not take into account changes in intragastric volume. Therefore, intragastric pH cannot be taken to reflect underlying changes in acid secretion.²² Other limitations of the continuous intragastric pH monitoring technique used in the present study include variations in pH resulting from the location of the probe within the stomach, the need for the probe to be in contact with the gastric mucosa or fluid, and the inability to identify episodes of gastroduodenal reflux.²³ Despite these limitations, continuous pH monitoring systems have become the gold standard for monitoring intragastric pH. These monitoring systems have been shown to be more precise than gastric aspiration, more physiologic because acid is not removed from the stomach, and more reliable because of their sampling frequency.^{20,24,25}

As previously reported,²⁶ basal gastric acid secretion in dogs is low, compared with humans. However, peak gastric acid secretion is considerably higher in dogs than in people. Results of the present study are in agreement with these findings. For example, median pH when food was withheld from the dogs was 4.44, but feeding a standard diet at fixed times was effective at stimulating gastric acid secretion (median pH, 1.30). It is for this reason that we elected to feed dogs in the present study when evaluating the effects of gastric acid suppressants.

In the present study, we elected to examine the effects of 2 commonly used H₂ receptor antagonists (ranitidine and famotidine) and 2 proton pump inhibitors (omeprazole and pantoprazole). At the time of the study, pantoprazole was the only proton pump inhibitor available in an injectable formulation in North America. Similarly, omeprazole was administered orally because it was only available in tablet form in North America at the time of the study. Because oral drug administration will itself cause gastric acid secretion by stimulating the cephalic phase of acid production,² use of omeprazole tablets may have altered the results of the present study somewhat. Although we considered giving placebo tablets to dogs during the weeks that they were receiving injectable medications, we thought that this would further confound our results.

Gastric parietal cells are stimulated to produce hydrochloric acid via 3 separate messengers (acetylcholine, gastrin, and histamine).²⁷ All 3 messengers act to stimulate the H⁺+K⁺-ATPase enzyme (proton pump) responsible for hydrogen secretion. The H₂ receptor antagonists block gastric acid secretion at the level of the H₂ receptor on gastric parietal cells, and even though the acetylcholine and gastrin pathways remain intact, inhibition of the histamine pathway affects the potentiation of the other 2 pathways and leads to significant gastric acid inhibition.²⁷ In contrast, proton pump inhibitors block gastric acid secretion at the level of the H⁺+K⁺-ATPase enzyme.

Dosages of gastric acid suppressants currently recommended in the veterinary literature have been extrapolated from dosages recommended for humans and have been calculated to inhibit maximally stimulated acid secretion by at least 50% throughout the

day.²⁸ However, the degree of gastric acid suppression necessary for various therapeutic effects in dogs is still undetermined.

In the present study, we found that administration of famotidine, pantoprazole, or omeprazole significantly suppressed gastric acid secretion, compared with administration of saline solution. No significant differences were noted in efficacy of the drugs when comparing measurements obtained on day 2 with those obtained on day 6.

Conversely, ranitidine had no significant effect on gastric acid secretion, compared with saline solution, suggesting that at the dosage used, it would be unlikely to have any beneficial effects on gastric ulcer prophylaxis or treatment. Increasing the dosing frequency (ie, administration every 8 hours instead of every 12 hours) or dose may improve its effects, as plasma ranitidine concentration has been shown to have a significant linear correlation with gastric acid inhibition in people.²⁹

In the present study, when comparing antisecretory drugs against each other, only omeprazole showed a significant improvement in gastric acid inhibition, compared with both H₂ receptor antagonists on day 2, as assessed by the percentage of time that the pH was maintained ≥ 3 . By day 6, no significant differences were found in any outcome measure (median intragastric pH, percentage of time intragastric pH was ≥ 3 , and percentage of time intragastric pH was ≥ 4) among famotidine, pantoprazole, and omeprazole. Previous studies^{7,11,30} have reported that proton pump inhibitors are more potent at inhibiting gastric acid secretion than are H₂ receptor antagonists; however, we did not find this to be true in the present study. Potency of the H₂ receptor antagonists relates to the extent to which they bind with the H₂ receptor,⁸ and famotidine is reported to be 8 to 9 times as potent as ranitidine.^{31,32} In the present study, at the dosages used, famotidine increased intragastric pH to a greater extent and for a longer time than did ranitidine.

Drug carryover effects were identified in the present study, with famotidine and pantoprazole having more pronounced carryover effects than ranitidine. For pantoprazole, a proton pump inhibitor, carryover effects were not unexpected, as this drug binds irreversibly to the proton pump.⁶ However, carryover effects with the H₂ receptor antagonists were unexpected and difficult to explain, and it is possible that other factors unrelated to drug administration (eg, environmental factors and acclimation of the dogs) may have accounted for the carryover effects. Regardless, our findings suggested that washout periods longer than 1 week be used. The 1-week washout period used in the present study was selected because it represented a minimum of 20 half-lives for all 4 drugs and because full restoration of gastric acid secretion has been demonstrated 1 week after administration of proton pump inhibitors has been discontinued.^{6,8} Regardless, the comparative aspects of the present study were not affected as these carryover effects were controlled for in the study design and statistical analyses.

When, at the end of the randomized controlled trial, after unmasking the study, we found that none of the 4 drugs resulted in an intragastric pH ≥ 3 for at least 75% of the time, we elected to perform additional studies to determine whether modifications in the administration protocol would improve gastric acid suppression. In particular, we assumed that gastric acid suppressants would be used most frequently in critically ill dogs that would not be receiving oral medications. For this reason, we elected to examine the effects of increasing the dosing frequency of famotidine, an injectable gastric acid suppressant, and the effects of twice-daily omeprazole administered as a suspension through a feeding tube. For the latter, omeprazole tablets were dissolved in bicarbonate, as described,¹⁸ to prevent degradation in the acid environment of the stomach; omeprazole is absorbed in the small intestine.³³ Omeprazole tablets^j were used as they were available in Canada at the time of the study, but omeprazole capsules^l would have been an alternative.

Increasing the frequency of famotidine administration from 2 to 3 times a day did not have any significant effects on suppression of gastric acid secretion in the present study. In contrast, when omeprazole was administered twice daily as a suspension, mean percentages of time that intragastric pH values were ≥ 3 and ≥ 4 were 90.9% and 78.3%, respectively. Omeprazole, administered twice daily as a suspension, was the only drug regimen that approached the potential therapeutic efficacy for healing of gastric-related disease when assessed by criteria used for human patients (pH ≥ 3 or ≥ 4 for approx 75% of the day.) Studies⁸ in people have documented that higher dosages of omeprazole provide a more predictable inhibition of gastric acid secretion. In addition, when higher doses are needed, twice-daily administration is recommended to achieve optimal gastric acid suppression.⁸

Adverse gastrointestinal tract effects were reported for multiple dogs in the present study when omeprazole suspension was administered every 12 hours but were not observed with any of the other drug formulations. These adverse effects may have been related to the greater frequency of omeprazole administration, although they have not been identified in toxicologic studies³⁴ during which much higher dosages were administered; other possible causes include the formulation of omeprazole, the addition of sodium bicarbonate, and the route or rate of drug administration. Gastroenteritis could not be ruled out; however, gastroenteritis was unlikely as the dogs remained bright and the adverse effects were seen randomly throughout the week. One dog vomited immediately after receiving the omeprazole suspension, and all adverse gastrointestinal tract effects resolved when drug administration was discontinued. Interestingly, vomiting was not reported in a study¹⁸ involving human patients receiving this same formulation.

Dogs in the present study were healthy and were fed a standard daily diet. Thus, results should be extrapolated with caution to ill, possibly anorectic, dogs that may have altered gastric acid secretion. It is also important to recognize that gastric acid suppressants

have been shown to act differently depending on whether gastric acid secretion is stimulated. In humans,⁸ proton pump inhibitors resulted in prolonged and highly effective inhibition of basal and stimulated gastric acid secretion, whereas H₂ receptor antagonists were more effective at inhibiting intragastric acidity during periods of basal acid secretion.

Finally, the optimal degree of gastric acid suppression in dogs has not been established. It is likely that in dogs, as in humans, gastric acid suppression should be tailored to suit the acid-related condition with consideration given to the extent and severity of the condition. Results of the present study suggest that various gastric acid suppressants, when administered at currently recommended dosages, have different degrees of gastric acid suppression in dogs.

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- a. Ingold bipolar electrode, MIC Medical Instruments Corp, Solothurn, Switzerland.
 - b. Gastrograph III, MIC Medical Instruments Corp, Solothurn, Switzerland.
 - c. Buffer solutions, Fisher Scientific, Nepean, ON, Canada.
 - d. Winreflux, MIC Medical Instruments Corp, Solothurn, Switzerland.
 - e. Iams maintenance dry original formula, Iams Co, Dayton, Ohio.
 - f. Iams biscuits small original, Iams Co, Dayton, Ohio.
 - g. Zantac, GlaxoSmithKline Inc, Mississauga, ON, Canada.
 - h. Pepcid IV, Merck Frosst Canada Ltd, Kirkland, QC, Canada.
 - i. PantolV, Altana Pharma Inc, Oakville, ON, Canada.
 - j. Losec, AstraZeneca Canada Inc, Mississauga, ON, Canada.
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