

## STANDARD ARTICLE

# A prospective, randomized, masked, placebo-controlled crossover study for the effect of 10 mg omeprazole capsules on gastric pH in healthy dogs

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## Abstract

**Background:** Enteric-coated omeprazole capsules are commonly used as a gastric acid suppressant in dogs. However, the efficacy of this formulation has not been evaluated for clinical use in dogs.

**Hypothesis/Objectives:** To evaluate the efficacy of a 10 mg PO omeprazole capsule (TriviumVet) undergoing FDA approval to increase gastric pH in dogs. We hypothesized that encapsulated omeprazole would significantly increase the gastric pH compared to placebo and reach pH goals extrapolated from people for the treatment of esophagitis and duodenal ulceration.

**Animals:** Six healthy research dogs.

**Methods:** Randomized, blinded, 2-way crossover study. Dogs were PO administered omeprazole at 0.5 to 1.0 mg/kg or placebo (empty gelatin capsules) twice-daily for 5 days. The intragastric pH was recorded on days 2 to 5 of treatment. Mean pH and the mean percentage time (MPT) intragastric pH was  $\geq 3$  or  $\geq 4$  were compared between and within treatment groups.

**Results:** Dogs treated with omeprazole had a significantly higher MPT  $\pm$  SD intragastric pH  $\geq 3$  (91.2%  $\pm$  11.0%),  $\geq 4$  (86.9%  $\pm$  13.7%) and mean  $\pm$  SD pH (5.4  $\pm$  0.8) than dogs treated with placebo (19.7%  $\pm$  15.5%, 28.3  $\pm$  20.7, and 2.4  $\pm$  1.0, respectively) ( $P < .001$  for all).

**Conclusions and Clinical Importance:** The 10 mg enteric-coated omeprazole capsule PO administered evaluated in this study is an effective gastric acid suppressant in healthy dogs.

## KEYWORDS

bravo monitoring, canine, gastric pH, proton pump inhibitor

**Abbreviations:** GI, gastrointestinal; MPT, mean percentage time; PPI, proton pump inhibitor.

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## 1 | INTRODUCTION

Inhibition of gastric acid production with proton pump inhibitors (PPIs) is central to the treatment of many gastric and proximal duodenal ulcerative diseases in dogs.<sup>1</sup> Veterinary recommendations for type and frequency of administration of PPIs are largely based on studies that used criteria developed for human patients with gastric acid-related disorders. These criteria include maintaining the gastric pH  $\geq 3$  and 4 for 75% and 67% of the day to promote healing of duodenal ulcers and gastroesophageal reflux disease, respectively.<sup>2,3</sup> To the authors' knowledge, there are only 2 studies evaluating the effect of PO administered omeprazole on gastric pH in healthy dogs without additional pharmacologic (eg, pentagastrin-stimulation) interventions.<sup>4,5</sup> The formulations that were evaluated in these studies included omeprazole tablets and reformulated paste, dosed once-daily, and an omeprazole suspension, dosed twice-daily. The omeprazole suspension, when PO administered twice-daily at 1 mg/kg, resulted in excellent acid suppression with a gastric pH  $\geq 3$  for approximately 90% of the day on day 2 of treatment.<sup>4</sup>

A wide range of over-the-counter (OTC), nonprescription formulations of omeprazole intended for human use are available; however, these products are often only available in sizes of  $\geq 20$  mg making optimal dosing of dogs  $< 20$  kg challenging. Enteric-coated omeprazole capsules offer more tailored dosing, but despite the widespread use of this formulation, there are no studies evaluating the effect of omeprazole capsules on gastric pH in dogs. Omeprazole capsules are generally comprised of a gelatin capsule containing multiple enteric-coated granules. Both omeprazole tablets and the enteric-coated granules contained within capsules consist of an inner drug core, a subcoating layer, and an exterior enteric-coating layer. The enteric coating is designed to be degraded at a specific pH such that the drug can avoid premature degradation in the stomach and be released and absorbed in the small intestine either immediately upon entering the intestine, or over the course of small intestinal transit. The enteric-coating characteristics, including thickness and polymer composition, determine the lag time before initiation of drug release and the subcoating characteristics affect the drug release rate.<sup>6</sup> In a recent study evaluating 1 branded, 1 generic, and several self-prepared omeprazole capsules with different drug coating materials, the drug's enteric-coated layer had a dramatic effect on *in vitro* drug release as well as the pharmacokinetics of PO administered omeprazole in beagle dogs.<sup>6</sup> The effect of the various products on increasing intragastric pH in dogs was not assessed. These results suggest a demand for further evaluation of the efficacy of encapsulated omeprazole in dogs and the need for a consistent and efficacious omeprazole product that can be easily dosed to a variety of dog sizes.

Accordingly, we evaluated the effect of oral administration of a novel, 10 mg enteric-coated omeprazole capsule undergoing FDA approval on gastric pH in healthy dogs. Additionally, we monitored for development of adverse effects as a result of omeprazole use. We hypothesized that the omeprazole capsule would significantly increase the gastric pH of dogs compared to placebo and achieve the aforementioned pH goals for the treatment of duodenal ulceration as defined for people.

## 2 | MATERIALS AND METHODS

### 2.1 | Study animals

We studied 6 healthy adult dogs from a research colony at North Carolina State University (3 spayed females and 3 neutered males; 4 Beagle dogs and 2 X hounds), aged 1.25-7.5 years (median, 4.5 years), weighing 10-18.9 kg (median, 11.9 kg), with body condition scores of 4-5/9 (median, 4.5), and a normal muscle condition score in all dogs. Dogs were excluded from the study if they had a history of clinical signs of gastrointestinal (GI) disease including vomiting, inappetence, diarrhea, or receiving any medications other than routine anthelmintic and heartworm preventative. Dogs also were excluded from the study if abnormalities were present on historical blood tests, if there were any physical examination findings suggestive of systemic or GI disease including low body or muscle condition score or abnormalities identified on abdominal palpation or thoracic auscultation. Finally, dogs were excluded if they had abnormalities present on baseline blood test results (ie, CBC, serum biochemistry profile, urinalysis) performed within 6 months of study entry. Animals were cared for according to the principles outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals (approved Institutional Animal Care and Use Committee protocol for this study #20-207-O).

### 2.2 | Study design

In a randomized, blinded, 2-way crossover study design, all dogs were PO administered noncompounded omeprazole (10 mg delayed-release omeprazole capsules; TriviumVet, Waterford, Ireland) at a median dosage of 0.86 mg/kg (range, 0.53-1.0 mg/kg) or placebo (identical empty gelatin capsules) twice-daily. All drugs were administered 30 minutes before feeding. All dogs were fed their normal diet (Exclusive adult dog food; Land O'Lakes, Inc, Arden Hills, Minnesota) throughout the study. Dogs were randomized to a treatment schedule by a random number generator, so that 3 dogs were randomized into each group. Dogs were medicated at approximately 7 am and 3:30 pm. The feeding schedule and dosage interval were maintained throughout the study period. Dogs had unlimited access to water during the pH monitoring period. Fecal consistency was graded from 1 to 7 on each day of each treatment period using a standardized fecal scoring system (Fecal Scoring System, Nestlé Purina PetCare Company, St. Louis, Minnesota). Diarrhea was defined as a fecal score  $> 4$ . Clinical signs, including changes in activity, food consumption, vomiting, and number of defecations, were recorded a minimum of q12h. An episode of inappetence was defined as consumption of  $< 50\%$  of the meal offered. Vomitus was evaluated for the presence of medication or the pH capsule when it occurred. A period of 10 days separated treatment groups.<sup>7</sup> Investigators were blinded to treatment group until the data collection and statistical analyses were completed.

## 2.3 | Intragastric pH monitoring

The pH capsule (Bravo pH calibration-free reflux capsule with delivery system, Medtronic, Minneapolis, Minnesota) was placed using radiographic guidance under sedation as previously described.<sup>8</sup> All pH capsules were linked to their associated receivers (Bravo reflux recorder, Medtronic) according to the manufacturer's instructions. On the second treatment day after an overnight fast, dogs were sedated with 5 µg/kg dexmedetomidine (Dexdomitor 0.5 mg/mL injection; Orion Pharma, Espoo, Finland) IV and 0.2 mg/kg butorphanol (Torbugesic 10 mg/mL injection; Zoetis Inc, Kalamazoo, Michigan) IV. The dogs were placed in left lateral recumbency. The pH capsule then was blindly introduced transorally into the proximal stomach and placed in the gastric fundus using radiographic guidance as previously described.<sup>8</sup> The location of each pH capsule was kept consistent in each dog among treatment groups by utilizing the markings on the capsule delivery device to measure the distance from the maxillary canine teeth to the area of capsule placement in the gastric fundus.<sup>8</sup> Sedation was reversed with atipamezole (Antisedan 5 mg/mL injection; Orion Pharma) IM after pH capsule placement. The pH capsule placement was repeated in the same manner for both treatments.

## 2.4 | pH recordings

Intragastric pH recordings were obtained telemetrically at 6-second sampling intervals. Twenty-four-hour intragastric pH recording was initiated immediately after placement and acquired continuously for up to 96 hours (treatment days 2-5). The corresponding data receivers were kept on the side of each dog's cage during the data acquisition phase. After data acquisition, the pH data were uploaded to the computer using a software package provided by the manufacturer (Reflux Software v6.1, Medtronic). Mean pH and mean percentage time (MPT) the intragastric pH  $\geq 3$  and  $\geq 4$  were calculated using statistical software (Prism 8, Graphpad Software, San Diego, California).

## 2.5 | Statistical analysis

A 2-factor repeated-measures mixed-effects crossover design and corresponding analysis of variance (ANOVA) was performed to evaluate mean intragastric pH, MPT intragastric pH  $\geq 3$ , and MPT intragastric pH  $\geq 4$ . Each response measure was analyzed using a repeated-measures mixed-model ANOVA to determine treatment, time (day of treatment), and treatment-by-time interaction. Unstructured Kronecker product variance/covariance structures were incorporated into each model. Tukey-Kramer *P*-value adjustments were applied to post hoc tests. A Shapiro-Wilk test for normality and QQ plots were used to evaluate normality of ANOVA residuals. Levene's equality of variances test was used to evaluate equality of treatment variances. Box-and-Whisker plots and studentized residual diagnostics were performed to evaluate each mixed model for the presence of

outliers. All statistical assumptions regarding normality and equality of variances were met. Statistical analysis was performed using commercial software (SAS software, version 9.4, Cary, North Carolina, Release TS1M6). Statistical significance was defined as  $P \leq .05$ . A power analysis was not performed before the study.

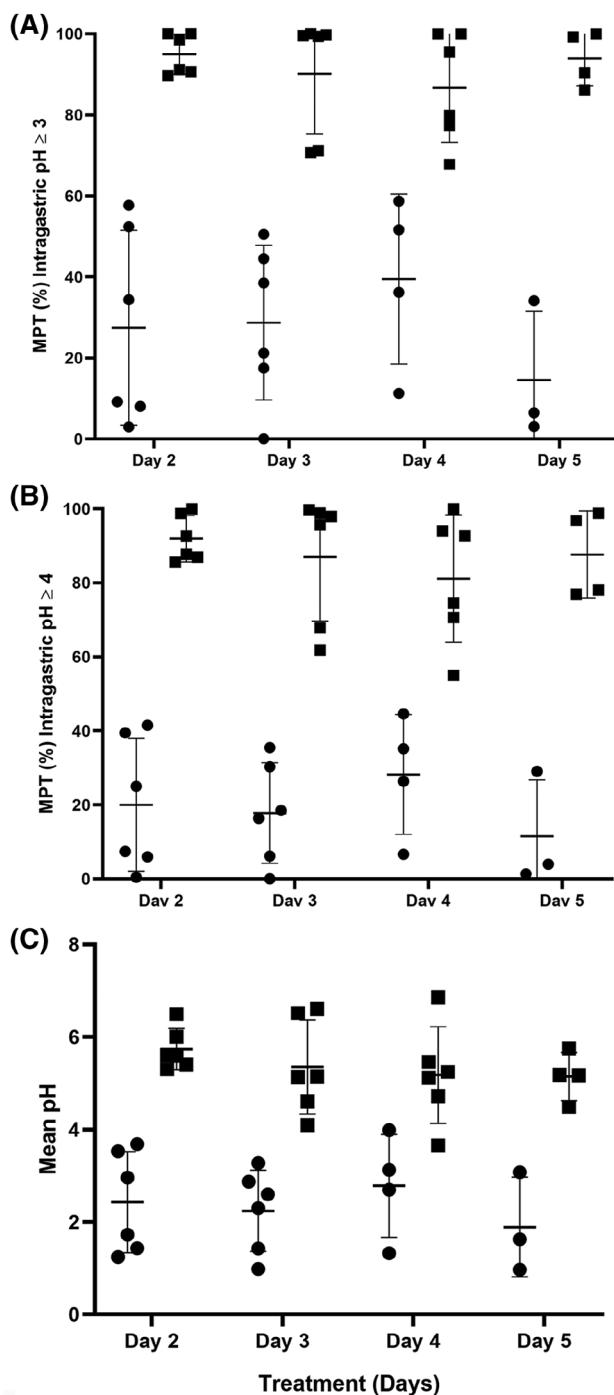
## 3 | RESULTS

### 3.1 | pH capsules and gastric pH recording

On 5 occasions, the pH capsule detached and exited the stomach before the end of the treatment period. This occurred in 3 dogs receiving placebo (2 dogs during day 4 and 1 dog on day 5) and 2 dogs receiving omeprazole (both on day 5). Therefore, data from these dogs were not included in the treatment comparisons on days in which the data were not available. Mean intragastric pH and MPT intragastric pH  $\geq 3$  and 4 are depicted in Figure 1. Significant differences in MPT intragastric pH  $\geq 3$ , 4, and mean pH were found between treatments ( $P < .001$ ). A significant treatment-by-time interaction was observed for MPT intragastric pH  $\geq 3$  ( $P = .04$ ). Post hoc tests revealed that omeprazole significantly increased MPT intragastric pH  $\geq 3$  on all days compared to placebo ( $P < .001$ , for all). After Tukey-Kramer *P*-value adjustments were applied, no significant differences in MPT intragastric pH  $\geq 3$  were observed over time within treatment ( $P \geq .1$ , for all). Furthermore, no main effect time differences or significant treatment-by-time interactions were observed in MPT of intragastric pH  $\geq 4$  ( $P = .42$ ,  $P = .07$ , respectively) or mean pH ( $P = .13$ ,  $P = .23$ , respectively).

### 3.2 | Adverse events

Ten dogs were evaluated before study onset. One dog was excluded because of the presence of suspected hepatic disease based on pre-study blood work. One dog was excluded because of the necessity for anticonvulsant medications. Two dogs were excluded because of the requirement for fish oil supplementation. Six dogs were enrolled in the study. All treatments were generally well tolerated. All dogs were bright and alert throughout the study period. All dogs ate all food offered at all meals. The total number of vomiting episodes during treatment periods was 3 (1 and 2 episodes in 2 dogs, each receiving omeprazole). All of the vomiting episodes occurred hours after medicating the dogs and did not contain food or visible medication in the vomitus. There was no significant difference in mean fecal score over time ( $P = .31$ ), between treatments ( $P = .06$ ), or observed via the treatment-by-time interaction ( $P = .18$ ). The mean  $\pm$  SD fecal scores for dogs treated with omeprazole or placebo for all treatment days were  $3.0 \pm 1.5$  and  $2.3 \pm 1.1$ , respectively. There were 13 episodes of fecal scores  $\geq 5$  among 4 dogs (3 episodes in 2 dogs receiving placebo and 10 episodes in 4 dogs receiving omeprazole). The remaining 2 dogs had normal feces throughout the course of the study.



**FIGURE 1** The mean percentage time (MPT, %) intra-gastric pH  $\geq 3$  (A),  $\geq 4$  (B), and mean intra-gastric pH (C) for all dogs PO administered 0.5 to 1.0 mg/kg twice-daily omeprazole or placebo (empty gelatin capsules) on treatment days 2 to 5. Horizontal and vertical lines represent the means and standard deviations, respectively, for each day. Individual dog data are represented by closed circles (placebo) or closed squares (omeprazole)

## 4 | DISCUSSION

Omeprazole is commercially available both as prescription only and OTC in a wide range of formulations including enteric-coated tablets,

capsules, and a powder for suspension. The OTC powder for oral suspension contains xylitol, which can be toxic to dogs and is not recommended for use. Omeprazole tablets have been evaluated in several studies and have been demonstrated to be efficacious in increasing the gastric pH of dogs<sup>4,5</sup> but are only widely available in a range of sizes (20-40 mg) that make targeted dosing difficult in dogs. The efficacy of omeprazole capsules in increasing gastric pH in dogs requires exploration.

Differences in enteric coating layer characteristics could result in differences in the drug's pharmacokinetic<sup>6</sup> and pharmacodynamic profile in dogs. There is no FDA, or other regulatory body, -approved omeprazole product for administration in dogs that would ensure consistency and quality of the product including an encapsulated formulation. In other countries such as Cambodia, generic omeprazole formulations have been demonstrated to vary widely because of the use of cheaper coating substitutes and, consequently, premature release of the drug in the stomach.<sup>9</sup> However, it should be noted that in a study evaluating 5 generic omeprazole products in the United States, all 5 products met the in vitro drug dissolution standards established by the United States Pharmacopeia.<sup>10</sup> In this study, we evaluated the use of a 10 mg omeprazole capsule from a single source (TriviumVet) undergoing FDA approval for use in dogs to explore 0.5 to 1.0 mg/kg tailored dosing and to evaluate the efficacy of the product in increasing gastric pH in dogs. We demonstrated that twice-daily oral administration of the noncompounded, 10 mg omeprazole capsule undergoing FDA approval at 0.5 to 1.0 mg/kg resulted in excellent gastric acid suppression in all dogs on all treatment days evaluated with the exception of 1 day for 1 dog. On treatment day 4, this dog had a MPT intra-gastric pH  $\geq 3$  and 4 of 67% and 55%, respectively. The encapsulated omeprazole achieved goals for the treatment of esophagitis and duodenal ulceration on days 2 to 3 and day 5 in this dog; thus, the reason for the drop in this dog's gastric pH on treatment day 4 is unknown and not thought to be related to a delay in achieving maximal efficacy of drug. Possible reasons for the drop in MPT intra-gastric pH  $\geq 3$  and 4 on this day include intraindividual variability and the prolonged dosing interval separating the evening and morning administration of drug.

Adverse GI effects are frequently reported in dogs after PPI administration, with the most common reported adverse events being vomiting and diarrhea.<sup>4,5,11</sup> Vomiting was limited to 3 episodes in 2 dogs receiving omeprazole. Overall, no significant differences in adverse events were identified between groups in this study and both omeprazole and placebo were well-tolerated. However, despite a lack of a significant difference in mean fecal score, it should be noted that there were more episodes of diarrhea during the omeprazole treatment group compared to placebo and the study was likely underpowered to identify such a difference.

This study was limited to a small sample of dogs that represented only 2 small- to medium-sized breeds. None of the dogs had signs of gastroesophageal disease. Additionally, the encapsulated omeprazole was not compared to other available omeprazole formulations. Thus, additional comparative studies are warranted to determine the efficacy of the encapsulated product in dogs with esophagitis or

ulcerative disease. The study was performed with a short (5-day) treatment period in which pH monitoring was initiated on day 2 of treatment. Although we cannot determine the pharmacodynamic effects of omeprazole on the first day of treatment, we demonstrate that the goals for the treatment of aforementioned goals in people<sup>2,3</sup> were achieved by day 2 with MPT  $\pm$  SD gastric pH  $\geq 3$  and 4 of 95%  $\pm$  5% and 92  $\pm$  6%, respectively. Thus, we believe that the drug works quickly and effectively. Additional studies are underway to determine the effect of the drug in the treatment of dogs with ulcerative disease. Based on the current study and goals described for the treatment of humans with acid-related disorders, we conclude that the 10 mg omeprazole capsule evaluated in this study is an effective and rapid-onset gastric acid suppressant in healthy dogs.

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#### CONFLICT OF INTEREST DECLARATION

L. Grubb is the CEO and founder of TriviumVet and S. Fitzgerald is the Head of Clinical Affairs at TriviumVet. M. K. Tolbert is a member of the TriviumVet scientific advisory board.

#### OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

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

The IACUC at North Carolina State University approved the protocol for this study (Approval #20-207-O).

#### HUMAN ETHICS APPROVAL DECLARATION

The authors declare human ethics approval was not needed for this study.

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