Pharmacokinetics and Acid Suppressant Efficacy of Esomeprazole after Intravenous, Oral, and Subcutaneous Administration to Healthy Beagle Dogs

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Background: Esomeprazole is an S-enantiomer of omeprazole that has favorable pharmacokinetics and efficacious acid suppressant properties in humans. However, the pharmacokinetics and effects on intragastric pH of esomeprazole in dogs have not been reported.

Objective: To determine the pharmacokinetics of esomeprazole administered via various routes (PK study) and to investigate the effect of esomeprazole on intragastric pH with a Bravo pH monitoring system (PD study).

Animals: Seven adult male Beagle dogs and 5 adult male Beagle dogs were used for PK and PD study, respectively.

Methods: Both studies used an open, randomized, and crossover design. In the PK study, 7 dogs received intravenous (IV), subcutaneous (SC), and oral doses (PO) of esomeprazole (1 mg/kg). Each treatment period was separated by a washout period of at least 10 days. Esomeprazole plasma concentrations were measured by HPLC/MS/MS. In the efficacy study, intragastric pH was recorded without medication (baseline pH) and following IV, SC, and PO esomeprazole dosing regimens (1 mg/kg) in 5 dogs.

Results: The bioavailability of esomeprazole administered as PO enteric-coated granules and as SC injections was 71.4% and 106%, respectively. The half-life was approximately 1 hour. Mean ± SD percent time intragastric pH was ≥3 and ≥4 was 58.9 ± 21.1% and 40.9 ± 17.3% for IV group, 75.8 ± 16.4% and 62.7 ± 17.7% for SC group, 88.2 ± 8.9% and 82.5 ± 7.7% for PO group, and 12.5 ± 3.6% and 3.7 ± 1.8% for baseline. The mean percent time with intragastric pH was ≥3 or ≥4 was significantly increased regardless of the dosing route (P < .05).

Conclusion: The PK parameters for PO and SC esomeprazole administration were favorable, and esomeprazole significantly increased intragastric pH after IV, PO, and SC administration. IV and SC administration of esomeprazole might be useful when PO administration is not possible. No significant adverse effects were observed.

Key words: Bravo pH; Intragastric pH; Proton pump inhibitor.

Omeprazole is widely used as a proton pump inhibitor (PPI) for treating and preventing acid-related diseases in human and veterinary medicine, and it is administered as a racemic mixture of 2 optical isomers: S-omeprazole (esomeprazole) and R-omeprazole.1,2 These 2 enantiomers are converted in the same proportions to an achiral active form in the acidic compartment of gastric parietal cells.3 Esomeprazole was developed as the first single optical PPI (2000, AstraZeneca) containing only S-isomer of omeprazole, the R-isomer being absent.3

Abbreviations:

| Abbreviation | Description                  |
|--------------|------------------------------|
| AUC          | area under the plasma concentration-time curve |
| AUMC         | area under the respective first moment-time curve |
| CL           | elimination clearance |
| C_{max}      | peak plasma concentration |
| F            | bioavailability |
| GERD         | gastroesophageal reflux disease |
| H2RA         | H2-receptor antagonist |
| MPT          | mean percent time |
| PPIs         | proton pump inhibitors |
| T_{1/2}      | terminal elimination half-life |
| T_{max}      | time until maximum concentration |
| V_{ss}       | volume of distribution at steady state |

Esomeprazole provides better acid control and more favorable pharmacokinetics (PKs) relative to currently used racemic PPIs in human.4–6 Treatment with a single oral dose of esomeprazole resulted in a greater total area under the plasma concentration-time curve (AUC) and a more rapid increase in gastric pH than the same dose of racemic omeprazole.3,6 In 8-week clinical trials involving patients with erosive esophagitis, the treatment group receiving esomeprazole showed significantly higher healing rates than patients receiving omeprazole or lansoprazole.5 In veterinary medicine, however, little information has been published about the PKs and acid suppressant efficacy of esomeprazole in dogs.7,8

Measuring intragastric pH has been widely accepted as a valid method for comparing and evaluating the efficacy of acid suppressants; however, the correlation
between increased intragastric pH and outcome of acid-related disorders has not been studied enough.\textsuperscript{1,5,6,8–12} The aspiration of gastric juices, the placement of a pH electrode through a gastric fistula, and the placement of an pH catheter have been used as methods for measuring gastric pH.\textsuperscript{7,8} Previous studies have reported that the aspiration is a relatively invasive technique that may alter gastric physiology, whereas catheterization poses risks of catheter migration and substantial discomfort.\textsuperscript{1,13} The Bravo\textsuperscript{4,5} pH monitoring system is a wireless radiotelemetric device used for prolonged monitoring of intraesophageal or intragastric pH that is minimally invasive and can avoid the discomforts associated with the previously mentioned methods.\textsuperscript{14}

The aims of the current study were to determine the PKs of intravenous (IV), subcutaneous (SC), and oral (PO) esomeprazole administration to healthy Beagle dogs, and the effects of IV, SC, and PO esomeprazole administration on intragastric pH.

Materials and Methods

Dogs

Twelve healthy adult male Beagle dogs were randomly divided into 7 for the PK group and 5 for the PD group. Seven Beagle dogs, aged 1–4 years (median 4 years) and weighing 8.9–11.7 kg (median 10.3 kg), were included in the PK study. Five adult male Beagle dogs, aged 2–6 years (median 3 years) and weighing 9.9–16 kg (median 11.5 kg), were included in the PD study.

Complete physical examinations, CBCs, and serum biochemistry tests were performed for each dog. The dogs presenting clinical signs of gastrointestinal diseases (vomiting, diarrhea, and anorexia) or abnormal blood profile results were excluded. The experimental dogs were housed individually in cages and fed a commercial dry dog food\textsuperscript{15} twice a day except during the treatment period, and water was offered ad libitum. The illumination (12-hour light/dark cycle), temperature (19–25°C), and relative humidity (>40%) of the animal room were controlled. This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals and was approved by the Institutional Animal Care and Use Committee of the Chungnam National University (approved No. CNU-100626).

Experimental Design

In the PK study, using an open, randomized, crossover design, the dogs received 1 mg/kg q 24 hours of esomeprazole via IV, SC, and PO administration. Each treatment period was separated by a washout period of at least 10 days. For parenteral administration, commercial esomeprazole sodium powder\textsuperscript{b} was reconstituted with 5 mL of normal saline according to the manufacturer’s guidelines and administered as an IV infusion over 3 minutes or as an SC bolus injection in the space between the cranial angles of the left and right scapulae. For PO administration of the 1 mg/kg dose, enteric-coated esomeprazole granules\textsuperscript{c} were measured into portions of 11 mg of granules per kg body weight because this amount contained 1 mg/kg of esomeprazole. After the portions were divided, all drugs were prepared as granules in capsules. Oral esomeprazole was administered once-daily followed by water, for 5 consecutive days. Each drug treatment was administered in the morning after overnight fasting. Water was offered 2 hours after administration, and food was given after collecting the last blood sample during each treatment period.

In the PD study, the effect of esomeprazole on intragastric pH was determined with a Bravo\textsuperscript{4,5} pH monitoring system.\textsuperscript{d} Using an open, randomized, crossover design, intragastric pH was recorded without medication (baseline pH) and after the 3 dosing regimens: IV, SC, and PO doses of esomeprazole (1 mg/kg q 24 hours). All drugs were administered in the same manner as in the PK study. Drugs were administered once daily (7:30 AM), and dogs were fed twice daily (8:30 AM, 8:30 PM) during the study. The baseline recording period and the 3 treatment periods (IV, SC, and PO day 5) were separated by a washout period of at least 10 days. Any medication taken by the experimental dogs was not allowed during the week before the experiment and during the treatment periods. To identify any adverse effects of esomeprazole in the dogs, clinical signs were recorded, including pain after IV infusion or SC injection, dermatological changes at the SC injection site and changes in appetite, vomiting, and the number of defecations and quality of feces, which were graded from 1 to 7 with a fecal scoring system.\textsuperscript{5}

Blood Sampling and Analytical Procedures

Blood sampling was conducted on study day 1 for the IV and SC treatments and on study days 1 and 5 for the PO treatment. Blood samples (1.5 mL) were collected from the jugular vein predosing and at 3 (IV only), 5 (IV and SC only), 10, 20, and 40 minutes, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours after drug administration. The collected blood samples were transferred to heparin tubes and centrifuged for 10 minutes at 1000 × g. The plasma was stored at −80°C until analysis. Predosing and at 10 hours, additional blood samples (1.5 mL) were collected for pre and post-treatment blood tests, including CBC, serum chemistry, and electrolyte analyzes.

The plasma concentration of esomeprazole was measured by HPLC/MS/MS. An aliquot (50 μL) of an internal standard solution (carbamazepine 10 ng/mL in acetonitrile) and 400 μL of acetonitrile were added to an aliquot (50 μL) of plasma to induce the precipitation of plasma proteins. The mixture was vigorously mixed for 10 minutes and then centrifugation at 17,054 × g for 10 minutes. An aliquot (5 μL) of the supernatant was directly injected into the HPLC/MS/MS system.

Chromatographic separation was performed in a reverse phase column\textsuperscript{e} with an Agilent 1200 HPLC system.\textsuperscript{6} Detection was conducted with a triple quadrupole tandem mass spectrometer system.\textsuperscript{6} The detection of the ions was performed by monitoring the transitions of m/z: 346.1 to 198.2 for esomeprazole and m/z: 237.2 to 194.2 for carbamazepine. The peak areas for all components were automatically integrated by Analyst software version 1.5.1.\textsuperscript{e}

Esomeprazole was separated by gradient elution, which is consisted of mobile phase A 0.1% formic acid and B 0.1% formic acid in acetonitrile. Gradient condition was detailed as follows: Total run time was 5 minutes. Initially, mobile phase B was sustained as 5% from 0 to 1 minute. Then, B was reached to 95% for the 0.5 minute. Then 95% of mobile phase B was maintained for 1 minute. Next, the mobile phase B was drawn back to 5% for 0.5 minute, and equilibrated as 5% for the 2 minutes. The flow rate was 300 μL per minutes, and column was set to room temperature. The retention times of esomeprazole\textsuperscript{6} and carbamazepine were 3.66 and 3.68 minutes, respectively. The calibration curve was obtained by a weighted (1/x²) least squares regression analysis of the peak area ratios (esomeprazole/carbamazepine) versus the nominal concentrations of the calibration standards (r = 0.9909). The quantifiable range for the plasma samples was confirmed to be from 0.5 to 1,000 ng/mL, and the validation values, including the precision (coefficient of variance <11.25%), accuracy (relative error <13.87%), and 10-fold dilution integrity (coefficient of variance <4.01% and relative error <1.28%) of the measurements, were within the acceptable ranges given by FDA guidelines.\textsuperscript{15}
Pharmacokinetic Analyzes

To estimate the PK parameters of esomeprazole, plasma concentration-time profiles were analyzed by a noncompartmental model analysis in WinNonlin® software version 4.1. The terminal half-life (\(T_1/2\)) was calculated as 0.693/\(k_e\), where elimination rate constant (\(k_e\)) is the slope of the log-linear portion of the concentration-time profile. To determine the elimination clearance (CL) and the volume of the distribution at steady state (\(V_{ss}\)) for esomeprazole, a moment analysis was carried out. The area under the concentration of esomeprazole in the plasma versus the time curve from time zero to infinity (\(\text{AUC}_{0-\infty}\)) and the area under the respective first moment-time curve from time zero to infinity (\(\text{AUMC}_{0-\infty}\)) were calculated by the linear trapezoidal rule and the standard area extrapolation method. The CL and \(V_{ss}\) for esomeprazole were calculated using the following equations:

\[
\text{CL} = \frac{\text{Dose}}{\text{AUC}_{0-\infty}} \tag{1}
\]

\[
V_{ss} = \frac{\text{MRT}}{\text{CL}} \tag{2}
\]

\[
\text{MRT} = \frac{\text{AUMC}_{0-\infty}}{\text{AUC}_{0-\infty}} \tag{3}
\]

The peak plasma concentration (\(C_{\text{max}}\)) and the time until maximum concentration (\(T_{\text{max}}\)) were directly determined from the plasma concentration-time curves. Bioavailability (F) was estimated by comparing the normalized areas under the plasma concentration-time curve (\(\text{AUC}_{0-\infty}\)) for PO and SC administration.

Measurement of Intragastric pH with the Bravo® pH Monitoring System

The attachment of the Bravo pH capsules was performed on the day before recording baseline pH and IV or SC administration and on day 4 of the oral treatment period. All dogs were fasted overnight before attachment and allowed to drink water until 2–3 hours before anesthesia. The dogs placed under general anesthesia (premedication, glycopyrrolate 0.011 mg/kg; induction, propofol 6 mg/kg; and maintenance, isoflurane) and placed in a left lateral recumbent position. Before the attachment, a gastroscopic evaluation was performed to examine the appearance of the entire gastric mucosa. If a gastric lesion (eg, an ulcer) was detected, the dog was excluded from the experimental population. All capsules were calibrated with buffer solutions at pH 1.07 and 7.01 before 306 attachment. The Bravo capsules were orally inserted with a delivery system (80 cm in length, with a diameter of 6 Fr.). Under gastroscopic guidance, the capsules were attached to the gastric fundic mucosa as previously described.1,26 A data receiver was attached to the cage, which remained within 1 m of each dog. The recording of pH data began 5 minutes before drug administration and continued at 6-second intervals thereafter for approximately 24 hours, while being transmitted to POLYGRAM NET® software.4 Raw data were extracted into a Microsoft® Excel spreadsheet for calculations of the percent time that the intragastric pH was \(\geq 3\) or \(\geq 4\) and that the intragastic pH was in 1 of 9 pH categories (0–1, 1–2, 2–3, 3–4, 4–5, 5–6, 6–7, 7–8, or 8–9).

Statistical Analysis

The PK parameters and pH data were analyzed by a statistical analysis program.29 All data represent the mean ± standard deviation (SD).

In the PK study, a paired t-test was used to compare (1) the mean \(C_{\text{max}}\), half-life and \(\text{AUC}_{\text{last}}\) (day 1 versus day 5) values to identify the presence of drug accumulation resulting from the repeated PO administration of esomeprazole, and (2) the results of the pre and postadministration blood tests.

In a second analysis, a repeated-measures ANOVA was used to compare the mean percent time (MPT) with intragastric pH \(\geq 3\) or \(\geq 4\) among the groups during the 24-hour period after drug administration. When a time effect or a time × treatment interaction was present, a paired t-test or a one-way ANOVA with a Tukey’s posthoc test, respectively, was conducted. The MPT with intragastic pH in 1 of the 9 pH categories (0–1, 1–2, up to 8–9) was analyzed by a one-way ANOVA with Tukey’s posthoc tests.

The normal distribution of the data was verified by the Shapiro-Wilk’s test. Nonparametric data were analyzed by the Mann-Whitney rank sum test and the Kruskall-Wallis test. Sphericity was evaluated via Mauchly’s test, and Tukey’s range test was performed for multiple comparisons. The level of significance was set at \(P < .05\).

Results

Adverse Effects

No clinically notable adverse effects were observed during both studies. Vomiting was observed once, and soft stools (fecal scores of 5 and 6) were observed twice during the PK study. One dog presented itching immediately after the SC injection of esomeprazole. Dermatological changes in the SC injection site were not observed for 7 days after drug administration. No significant changes were observed in the results of the CBC, serum chemistry, and electrolyte tests between the pre and postadministration times except for the RBC count, platelet (PLT) count, and chloride levels. Postadministration values for RBC counts and chloride levels were slightly lower than the predadministration values (\(\text{preRBC}–\text{postRBC}, 0.43 \pm 0.72 \times 10^9/L\), \(P = .042\); \(\text{preCl}–\text{postCl}, 4.36 \pm 2.12 \text{mmol/L, } P < .001\)), although the postPLT count was higher than the prePLT count (\(\text{prePLT}–\text{postPLT}, –52.36 \pm 64.51 \times 10^9/L, P = .010\)).

During the 24-hour recording of intragastric pH, all dogs presented with good appetites, and no changes were observed in food intake. Vomiting was observed on 2 occasions (1 at baseline and 1 after IV administration). Because no defecation was observed in 7 of the 20 cases, the data for this parameter were insufficient for a statistical analysis. Fecal scores ranged from 1 to 3 (mean ± SD, 2.04 ± 0.43).

Pharmacokinetics of Esomeprazole

The PK parameters are presented in Table 1, and the plasma concentration profiles of the esomeprazole in the dogs are detailed in Figure 1. Differences in the \(\text{AUC}_{0-\infty}\) and half-life values were not significant \((P = .25\) and \(P = .13\), respectively); however, significant differences were observed for \(C_{\text{max}}\) among the administration routes \((P = .009\)).

After the 1 mg/kg SC bolus injection, the half-lives for the 1 mg/kg IV infusions and SC injections were 0.73 hours and 0.9 hours, respectively, but no significant difference in these half-lives were observed \((P > .05)\). The esomeprazole bioavailability after SC injections was 106%.
For the PO treatment, the peak plasma concentration was reached 1.81 hours after a single administration of enteric-coated esomeprazole granules. The $C_{\text{max}}$ of the PO esomeprazole treatment was significantly lower than that of the IV ($P = .004$) treatment, and the bioavailability was 71.43%. After repeated PO administrations of esomeprazole (1 mg/kg, once daily), the $T_{\text{max}}$ on day 5 was 2.23-fold faster than on day 1 (0.81 and 1.81 hours, respectively; $P = .022$). However, no significant differences were observed in the $C_{\text{max}}$ ($P = .082$), AUC$_{\text{last}}$ ($P = .71$), and half-life ($P = .50$) values between day 1 and day 5.

### Use of the Bravo pH Monitoring System

The gastric mucosa of all dogs had a normal appearance, and no significant changes were observed in the gross appearance of the gastric mucosa during the entire experimental period. No capsules were found from prior attachments, and mild erosive lesions, which were suspected of resulting from the detachment of the capsule, were found in 2 of the dogs.

Twenty Bravo capsules were successfully attached to the fundic mucosa (19 capsules to the greater curvature and one capsule to the lesser curvature of fundus). During procedure, the length of inserted delivery device ranged from 42 to 47 cm (mean 45 cm) at rostral point of mouth. Endoscopic procedure times ranged from 7 to 30 minutes and took 13 minutes on average. The pH data were recorded for approximately 477 hours, which represented 286,040 pH measurements. In total, 8,853 lost pH measurements were identified, and the mean percent of missing data was 3.07%.

### Intragastric pH Values

The MPT values that pH was $\geq 3$ or $\geq 4$ were detailed in Table 2. All esomeprazole treatment (IV, SC, and PO) groups, compared with the baseline group, exhibited a significantly higher MPT with intragastric pH $\geq 3$ or $\geq 4$ during the 24 hours after treatment ($P < .05$). Among all 3 treatment groups, the differences in MPT with intragastric pH $\geq 4$ were not significant ($P > .05$); however, the MPT with the intragastric pH $\geq 3$ differed significantly between the IV and PO groups ($P = .019$).

For a comparison of the time effect and treatment effect on intragastric pH, the MPT with intragastric pH $\geq 3$ or $\geq 4$ during the first 12 hours after treatment and during the remaining 12 hours were analyzed (Fig 2). Comparing MPT values that pH was $\geq 3$, a significant time effect was observed within the groups ($P = .001$), and a significant time × treatment interaction was
Table 2. Effect of esomeprazole on intragastric pH for various administration routes.

| Treatment | Mean ± SD  | P value |
|-----------|-----------|---------|
| MPT pH ≥3 for 24 hours |  |  |
| Baseline | 12.54 ± 3.62 | — |
| IV | 58.88 ± 21.08 | .043 |
| SC | 75.79 ± 16.42 | .004 |
| PO Day 5 | 88.16 ± 8.91 | <.001 |
| MPT pH ≥4 for 24 hours |  |  |
| Baseline | 3.73 ± 1.81 | — |
| IV | 40.85 ± 17.25 | .049 |
| SC | 62.68 ± 17.68 | .010 |
| PO Day 5 | 82.54 ± 7.76 | <.001 |

MPT, mean percent time; IV, intravenous administration; PO, oral administration; SC, subcutaneous administration.

All data represent the mean percent time that the intragastric pH was ≥3 or ≥4 during the 24 hours after treatment. P values represent comparisons of the three dosing groups to the baseline group.

observed (P = .030), but a significant difference in MPT between the first 12 hours after treatment and during the remaining 12 hours was only identified in the IV group (P = .017). Comparing MPT values that pH was ≥4, a significant time effect was identified (P = .021), whereas the MPT values for the treatment groups (IV, SC, PO) were not significantly different.

The distributions of intragastric pH levels for the 24 hours after treatment in all groups are presented in Figure 3. In the pH categories 0–1, 1–2, 2–3, 3–4, and 4–5, no significant differences were observed among any of the groups (all P values <.041). For the pH category 0–1, the MPT for the baseline group was higher than the values for the treatment groups. The MPT values for the pH categories 6–7, 7–8, and 8–9 did not meet the assumption of a normal distribution, and significant differences were not identified after a nonparametric analysis.

Discussion

Esomeprazole is a single optical isomer of omeprazole that is used in veterinary medicine; although there is a lack of literature on its PK and PD properties. However, PK information relating to the use of esomeprazole in veterinary medicine is not available, and little published support exists regarding esomeprazole dosages in dogs.17 IV administration of esomeprazole (1 mg/kg) and cisapride (1 mg/kg) 12–19 hours and 1–1.5 hours before anesthesia resulted in decreased gastroesophageal reflux.1 However, this evidence is insufficient to support a dosage regimen for oral and parenteral esomeprazole administration in dogs.15 The present study aimed to compare the differences in the PK parameters and the efficacy of intragastric acid control among various esomeprazole administration routes. The results demonstrate that esomeprazole administration significantly increases the intragastric pH in dogs.

In human clinical trials, the percent time that the gastric pH is above 3 or 4 is typically used as a surrogate parameter for evaluating patients with gastroesophageal reflux disease (GERD) or with peptic ulcers, respectively.18 The duration for which the gastric pH is above 4 has been shown to have a direct relationship to the healing rate in GERD patients, and maintaining the intragastric pH above 4 for at least 16–18 hours is an important therapeutic target for treating these diseases.9,20 In veterinary medicine, however, no specific standards exist for the duration of drug use or target intragastric pH levels; therefore, MPT for which the pH was ≥3 or ≥4 were considered for dogs as previously reported.1,11,21

In the current study, the MPT with pH ≥3 or 4 in the IV group for the 24 hours after treatment was 58.88 ± 21.08% and 40.85 ± 17.25%, respectively. Although these results do not meet the criteria for humans, aspects of parenteral administration may support the potential application of esomeprazole via IV infusions in emergency cases. The short half-life (0.73 hours) and lower MPT values during the remaining 12 hours, compared with the values for the first
12 hours after treatment (Fig 2) indicate that a single IV infusion is not sufficient to maintain an increase in gastric pH for 24 hours. PPIs need time to reach their maximum efficacy because it takes time for the drug to accumulate in newly recruited parietal cells, and to maintain a steady state. In a human study, it was reported that the intragastric pH value fell below 4 after 15 hours and became unstable after a single IV injection of 40 mg esomeprazole, compared to twice-daily administration and 24-hour infusion groups. A recent study reported that esomeprazole inhibited gastric acid secretion in a dose-dependent manner and the MPT that pH ≥ 4 was 59% after single administration of 1.6 mg/kg esomeprazole in dogs. We presume that repetition of esomeprazole administration or an increase in dose may improve the MPT values, although the further study is needed to identify optimal dose regimen for dogs. CYP2C19 and CYP3A4 are associated with the metabolism of esomeprazole in people, and CYP1A1/2 and CYP2D15 are associated in dogs. Repeated PO administration of esomeprazole has been shown in human studies to result in an increase in its plasma concentration because of the inhibition of CYP2C19. One study reported that the AUC of repeated PO doses was 2.4-fold higher than that of a single 40 mg PO dose, suggesting that an accumulation of esomeprazole is expected to occur after repeated oral dosing. However, in this current study, the PK properties of esomeprazole in Beagles were slightly different from those observed in human studies. Although the AUC ratio and C_max ratio for day 5 versus day 1 were 1.06 and 1.30, respectively, no significant difference was observed between the single and repeated dosing results. These results imply that the short-term use of esomeprazole poses a low risk of plasma accumulation in dogs. According to a previous study, 3–5 days of administration are required to reach the maximum efficacy of omeprazole for reducing gastric acid. Thus, the differences in efficacy between single and repeated PO doses are thought to be associated with the saturation of gastric proton pumps rather than with PK differences after repeated PO administration.

Oral administration of esomeprazole as an enteric-coated granule for 5 consecutive days significantly increased the intragastric pH of the dogs in this study. The MPT with pH ≥ 4 was 82.54 ± 7.76% during the 24 hours after treatment and included an approximately 17-hour period during which the pH was ≥ 4. This result was enough to meet the therapeutic criteria previously described for humans. Previous study to evaluate efficacy of oral omeprazole reported that the MPT with pH ≥ 4 was 52 ± 17% and 44 ± 18% after treatment with an omeprazole tablet (1.5–2.6 mg/kg q24 hours) and a reformulated omeprazole paste (1.5–2.6 mg/kg q24 hours), respectively.

**Fig 3.** Distribution of the intragastric pH levels in the baseline group (A) and the treatment group after a single IV (B) or SC (C) and repeated PO (D) administration of esomeprazole. Each circle indicates the mean ±SD percent time that the intragastric pH was in 1 of 9 pH categories. *P < .05, indicates a significant difference from the baseline group.
people has been reported to be higher than that of omeprazole of the same dose. The efficacy of esomeprazole in suppressing gastric acid is closely related to the subject’s total exposure to the drug (ie, the AUC), and for that reason, esomeprazole has been shown to result in better acid suppression than omeprazole of equal doses in human studies. This difference in efficacy between the current study and a previous study may be due to the higher AUC for esomeprazole than for omeprazole, and the difference in study design and formulations (enteric-coated granules versus a delayed-release tablet), or it may due to the small study population and inclusion of only 1 breed in this study.

The PKs of SC esomeprazole administration have not been reported in either human or veterinary medical studies, although SC infusions of omeprazole in 2 elderly patients for whom PO administration was impossible have been reported. The SC group, which included rapid absorption (T\textsubscript{max} 0.38 ± 0.13 hour) and a high bioavailability (106%) after SC esomeprazole injections in dogs.

Subcutaneous esomeprazole injections were well tolerated. The pH of the reconstituted esomeprazole solution used for the SC injections ranged from 9 to 11, depending on the reconstitution volume. Because the alkaline pH of solution may cause dermatological problems at the injection site, an examination of the injection site was conducted during the 7 days after administration. The only recorded adverse effect was the itching observed in a dog immediately after the injection; other dermatologic signs were not observed. Thus, SC injections of esomeprazole for short-term use may be useful when PO and IV administration are not possible.

The current study, determines the PK profiles and effects on intragastric pH of esomeprazole after IV, PO, and SC administration. In conclusion, the PK parameters of esomeprazole associated with various administration routes were favorable; furthermore, repeated PO esomeprazole administration resulted in a significant increase in the intragastric pH. The IV and SC administration of esomeprazole might be useful in emergency cases, although once-daily dosing would not be enough. Esomeprazole administered as enteric-coated granules or as a reconstituted IV solution were well tolerated, and notable adverse effects were not observed.

The limitation of this study small population of 1 breed was used in this study. As the breed-related metabolic differences for esomeprazole in dogs have not been specifically studied, the translation of these results to other breeds should be considered with caution.

\textbf{Footnotes}

\begin{itemize}
\item \textsuperscript{a} Nutrena\textsuperscript{®} Perfect Active, Seongnam, South Korea
\item \textsuperscript{b} Nexium\textsuperscript{®} I.V. 40 mg/vial, AstraZeneca, Södertälje, Sweden
\item \textsuperscript{c} Medtronic, Fridley, MN, USA
\item \textsuperscript{d} Nestle’ Purina PetCare Company, St. Louis, MO, USA
\item \textsuperscript{e} E7906-50MG, Sigma Aldrich, St. Louis, MO, USA
\item \textsuperscript{f} Applied Biosystems/MDS SCIEX, Santa Clara, CA, USA
\item \textsuperscript{g} Applied Biosystems/MDS SCIEX, Foster City, USA
\item \textsuperscript{h} i Applied Biosystems/MDS SCIEX, CA, Foster City, USA
\item \textsuperscript{i} Microsoft Office Professional Plus 2016, Microsoft Corp., Redmond, WA, USA
\item \textsuperscript{j} IBM\textsuperscript{®} SPSS\textsuperscript{®} Statistics 22, IBM Corp., Armonk, NY, USA
\end{itemize}

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\textbf{Off-label Antimicrobial Declaration}: Authors declare no off-label use of antimicrobials.

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