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Ultrasonographic assessment of the effect of metoclopramide, erythromycin, and exenatide on solid-phase gastric emptying in healthy cats

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Abstract

Background: Available data on the effect of gastrointestinal motility-modifying drugs in cats are limited. Most recommendations for drug usage and dosage are based on collective clinical experience.

Objectives: To assess the effects of metoclopramide, erythromycin, and exenatide on gastric emptying (GE) and gastric motility in comparison to placebo. We hypothesized that metoclopramide and erythromycin would have prokinetic gastric effects, whereas exenatide would prolong GE times and decrease the motility index (MI) of antral contractions.

Animals: Eight healthy domestic shorthair cats.

Methods: Each cat had 4 separate ultrasonographic assessments. In a prospective, randomized, double-blind, 4-way crossover design, cats received placebo, metoclopramide, erythromycin, or exenatide for 2 days followed by a minimum 5-day washout period. Ultrasonographic GE times and MI were compared to placebo.

Results: When compared to placebo, the rate of GE was significantly faster after administration of metoclopramide and erythromycin. Significant differences were found at all fractions of GE after administration of erythromycin and all but 1 fraction after metoclopramide when compared to placebo. The rate of GE in the first half of the GE curve was significantly slower after exenatide administration. The total area under the MI curve was significantly larger after administration of metoclopramide and erythromycin than after placebo.

Conclusions and Clinical Importance: Metoclopramide and erythromycin shorten GE times and increase the MI of antral contractions, thus having a prokinetic effect in the stomach of healthy cats, whereas exenatide causes an initial delay in GE.

KEYWORDS

antral area, gastrointestinal motility disorder, motility index, ultrasound

Abbreviations: AUC, area under the curve; BCS, body condition score; BW, body weight; CA, amplitude of antral contractions; CF, frequency of antral contractions; DM, diabetes mellitus; GE, gastric emptying; GET, gastric emptying time; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; MI, motility index; MMC, migrating motor complex; T2DM, type 2 diabetes mellitus.

1 | INTRODUCTION

Gastric emptying (GE) is a complex process in cats and other species that is controlled and affected by many physiologic, dietary, pharmacologic, and pathologic factors.[1-6] Abnormal GE is associated with clinical signs such as vomiting, anorexia, nausea, and abdominal distension and discomfort, which are known to have a negative impact on quality of life. Chronic vomiting is a commonly observed clinical problem in cats, and abnormal gastrointestinal (GI) motility likely is involved in the pathogenesis in a substantial number of cats.[7] Gastrointestinal motility disorders in cats present both a diagnostic and therapeutic challenge and are likely under recognized in feline practice. Management of nonobstructive gastric motility disorders usually includes treatment of the primary disorder if identified, dietary modification, and administration of motility-modifying drugs.[7]

Published data on the effects of motility-modifying drugs in healthy cats are limited, and are almost nonexistent for cats with GI motility disorders. Therefore, most recommendations for drug usage and dosage are based on collective clinical experience.[7] Metoclopramide was shown to cause antral contractions in anesthetized healthy cats.[1] Its effects on GI motility and gastric emptying time (GET) have not been evaluated in nonanesthetized cats. Erythromycin is a motilin agonist that initiates interdigestive type III migrating motor complexes (MMCs) and is commonly used in dogs as a prokinetic.[8-10] No studies have evaluated the effects of erythromycin on GE or small intestinal transit time in cats.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the GI tract in response to food intake. Incretins have been the focus of recent studies because of their beneficial role in glucose homeostasis and in the treatment of type 2 diabetes mellitus (T2DM). Additionally, GLP-1 analogs are reported to slow GE, induce satiety, and promote weight loss in people.[11] The ability of GLP-1 agonists to decrease postprandial glycemic excursions appears to be related to their effect on GE, and this effect may represent the predominant mechanism of action.[12] The effects of incretins and their analogs on glucose homeostasis and body weight recently have been investigated in healthy cats and a cohort of diabetic cats,[13-16] but their effects on GI motility have not been evaluated.

Although several methods can be used to assess gastric motility, we recently reported good correlation between the rates of solid-phase GE measured using ultrasonography and radionuclide scintigraphy in healthy cats. We also found good correlation between the antral motility index (MI) measured using ultrasonography and GE assessed by scintigraphy.[17]

The aim of this prospective, randomized, double-blind, crossover study conducted in healthy cats was to assess the effects of metoclopramide, erythromycin, and exenatide on GE and gastric motility in comparison to placebo. We hypothesized that metoclopramide and erythromycin would increase the rate of GE and antral motility (ie, prokinetic effect), whereas exenatide would slow GE and decrease antral motility.

2 | MATERIALS AND METHODS

2.1 | Animals

Eight healthy, purpose-bred domestic shorthair cats were used in this study. The cats were acclimatized to individual housing, in their feeding regimen, and the handling and restraint necessary to obtain ultrasound images for 3 weeks before beginning the study. Only cats deemed healthy based on physical examination, CBC, serum biochemistry profile, serum total thyroxine concentration, and abdominal ultrasound examination were included in the study. Body condition score (BCS) was recorded for the cats by using a 9-point system (1 = extremely thin, 5 = optimal, and 9 = obese).[18] Cats were fed ad libitum and group-housed in 2 groups of 4 when not being prepared or evaluated. They were individually housed as needed to allow for fasting. All animal use was approved by the Louisiana State University Institutional Animal Care and Use Committee and the experiment was performed in an Association for Assessment and Accreditation of Laboratory Animal Care International accredited facility.

2.2 | Study design

In a prospective, randomized, double-blind, 4-way crossover design, cats received placebo (saline SC [same volume as metoclopramide injection] and PO [same volume as erythromycin PO solution]), metoclopramide (0.5 mg/kg SC q8h), erythromycin (1 mg/kg PO q8h), or exenatide (1.2 μg/kg SC q12h) for 2 consecutive days before ultrasound examination. Evaluations were followed by a minimum 5-day washout period, which exceeded 10 half-lives for all drugs used. Cats were randomized to treatment group using a random number generator. All sonographic evaluations were completed within 5 weeks.

2.3 | Test meal

The test meal for the ultrasound examinations consisted of a combination of a maintenance laboratory diet (LabDiet 5003-Laboratory Feline Diet, LabDiet, St. Louis, Missouri) and 1 teaspoon of a canned cat food (Purina Proplan Focus Chicken & Liver Entrée, Classic, Nestle Purina PetCare Company, St. Louis, Missouri). The test meal provided approximately 20% of the estimated daily energy requirement of each cat, as determined on the basis of the following equation: $70 \times BW^{0.75}$, where BW is the body weight (in kilograms) of the cat.

2.4 | Ultrasonography

Cats were fasted overnight for 18 hours before the examinations. The procedure was postponed and rescheduled if a cat did not consume at least 75% of the test meal within 15 minutes. All sonographic examinations were performed by the same sonographer (R. H.) using a 12 MHz linear array transducer (Hitachi Noblus, Hitachi Aloka Medical America

Inc, Wallingford, Connecticut) as previously decribed.[17] Briefly, cats were examined in dorsal recumbency with the transducer positioned on midline just caudal to the xiphoid. The gastric antrum was consistently identified as a round or oval-shaped structure during the sonographic examination in all cats. In preprandial images in which the stomach was empty, the lumen and the rugal folds had a cartwheel-like appearance. Distension caused by the test meal allowed visualization of the lumen as a hyperechoic region. Rarely, gas in the lumen caused distal acoustic shadowing, which obscured the distant wall of the stomach. The cross-sectional areas of the relaxed and contracted antrum were measured by tracing its serosal side with the machine's built-in caliper. If acoustic shadowing of intraluminal gas obscured the distant wall, the measurement was made by assuming the antrum had a round to oval shape. Measurements of antral area (cm^2) were obtained for 3 contractions at each time point, and the mean of the 3 measurements was used for statistical analysis. Antral area measurements were performed before ingestion of the test meal (baseline), after eating (time 0), then at 15, 30, and 60 minutes for the first hour, then at 30-minute intervals for a total of 480 minutes. The initial postprandial measurement (time 0) was performed immediately after consumption of all of the test meal or 15 minutes after food was offered if the meal was not completely consumed. The baseline antral area was subtracted from each subsequent measurement and the results were divided by the maximum area obtained during the examination. All measurements were expressed as a percentage of the maximum antral area and plotted against time. The total area under the curve (AUC) was calculated for the 480-minute period and GET for each given emptying stage (25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, and 90%) was determined using commercially available software (R version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria).

To assess antral motility, amplitude and frequency of antral contractions were measured at the same time points. The amplitude of antral contraction (CA; difference of gastric antrum cross-sectional area in relaxed state and contracted state divided by cross-sectional area in relaxed state) was determined on 3 separate contractions for each time point. Additionally, the frequency of contractions (CF) was assessed over a 2-minute period. A MI was calculated by multiplying mean amplitude by CF for each time point and plotted against time. The total AUC was calculated for the 480-minute period of the MI, CA, and CF curves for each treatment (R version 3.2.2, The R Foundation for Statistical Computing).

2.5 | Statistical analysis

The normality of data distribution was tested using the D'Agostino and Pearson omnibus normality test, and all data were normally distributed (GraphPad Prism, GraphPad Software Inc, La Jolla, California). Unless otherwise stated, data are reported as means and standard deviations. A mixed model ANOVA was used to assess the difference in amount of food consumed and time required for test meal consumption between drugs (JMP Statistical Discovery, SAS, Cary, North Carolina). A mixed model ANOVA with cat as a random effect and treatment as fixed effect also was used to assess the difference in each fractional GET, MI, CA, and CF at each time point and MI AUC, CA AUC, and CF AUC between drugs. Post hoc pairwise comparisons were examined using Tukey's test as appropriate (JMP Statistical Discovery, SAS). Two statistical software programs were used as appropriate (GraphPad Prism, GraphPad Software Inc; JMP Statistical Discovery, SAS), and a value of $P < .05$ was considered significant.

3 | RESULTS

Five cats were neutered males and 3 cats were spayed females, with a mean age of 6.6 ± 2.9 years (range, 4.5-11.5 years) and a mean BW of 6.2 ± 1.5 kg (range, 4.5-8.6 kg). The median BCS was 7/9 (range, 5/9-9/9). All cats consumed at least 87.3% of the test meal voluntarily within 15 minutes. The median amount of food consumed during the trials was not statistically different ($P = .14$) and was 100% for placebo (range, 93%-100%), metoclopramide (range, 87.3%-100%), erythromycin (range, 98%-100%), and exenatide (range, 91.1%-100%). The time required for test meal consumption (placebo, 7.9 ± 6 minutes [range, 2-15 minutes]; metoclopramide, 9.3 ± 4.9 minutes [range, 2-15 minutes]; erythromycin, 6.1 ± 4.1 minutes [range, 2-15 minutes]; and exenatide, 10.4 ± 5.3 minutes [range, 2-15 minutes]) was not statistically different ($P = .07$).

The highest percentage of the maximum antral area occurred after food consumption and was followed by a continuous decrease in area over time (Figure 1). The time to the highest percentage of the maximum antral area was significantly longer after exenatide ($P = .04$) compared to placebo.

Group means and standard deviations for fractional GE times for each stage of GE are shown in Table 1. The rates of GE after administration of metoclopramide were significantly faster than after placebo at all fractions of GE but one (25, 30 and 40-90% fractional GE,

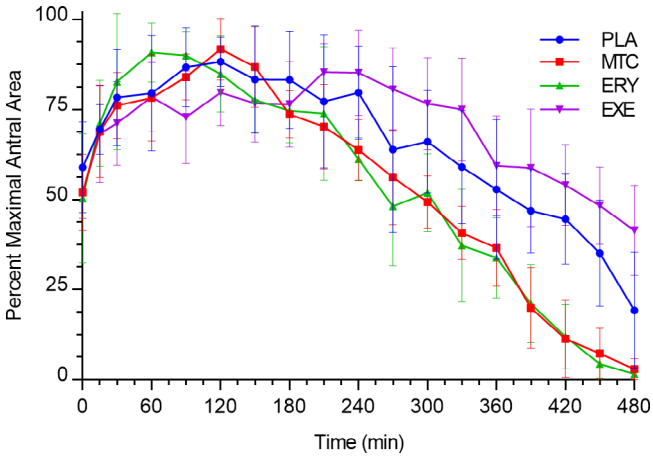

FIGURE 1 Cumulative sonographic measurements after placebo and each drug (metoclopramide, erythromycin, exenatide) expressed as a percentage of the maximal antral area plotted against time after test meal ingestion. Mean values with SD in 8 healthy domestic shorthair cats are shown

TABLE 1 Group means and standard deviations for sonographic gastric emptying times for each stage of GE after placebo and each drug (metoclopramide, erythromycin, exenatide) in 8 healthy domestic shorthair cats

	GE stage												
	25%	30%	35%	40%	45%	50%	55%	60%	65%	70%	75%	80%	85%	90%
GET placebo (min)	98.8 ± 16.6	116.9 ± 19.6	134.6 ± 22.5	152.8 ± 25.4	171.7 ± 28.4	191.1 ± 31.2	210.6 ± 33.3	230.6 ± 34.5	251.4 ± 35.8	273.7 ± 38.7	297.6 ± 40.1	324.2 ± 39.1	351.1 ± 39.5	384.4 ± 33.3
GET metoclopramide (min)	83.3[a] ± 6.8	99.4[a] ± 7.2	114.9 ± 8.3	129.6[a] ± 8.5	145.1[a] ± 9.5	161.1[a] ± 11.6	178.1[a] ± 14.2	195.5[a] ± 16.5	213.5[a] ± 18.0	232.9[a] ± 18.6	254.6[a] ± 19.6	278.3[a] ± 21.1	304.6[a] ± 23.3	334.4[a] ± 25.3
GET erythromycin (min)	78.7[a] ± 9.0	93.3[a] ± 9.4	108.4[a] ± 10.6	124.1[a] ± 12.6	140.1[a] ± 14.8	156.9[a] ± 16.7	174.7[a] ± 18.5	192.2[a] ± 20.5	209.3[a] ± 22.8	227.5[a] ± 25.9	248.4[a] ± 27.5	272.2[a] ± 25.9	297.6[a] ± 27.2	329.5[a] ± 22.8
GET exenatide (min)	114.3[b] ± 11.3	135.0[b] ± 14.6	157.8[b] ± 17.2	180.0[b] ± 20.0	200.8[b] ± 21.6	221.6[b] ± 23.0	240.9 ± 23.0	259.8 ± 23.4	280.4 ± 22.8	302.8 ± 22.0	325.1 ± 22.1	348.9 ± 21.4	376.9 ± 18.5	407.2 ± 12.6

Abbreviations: GE, gastric emptying; GET, gastric emptying time.

[a]Significant differences were found at all fractions of GE after administration of erythromycin and all but 1 fraction after metoclopramide when compared to placebo (35% fractional GE, P = .05).

[b]The rate of GE after administration of exenatide was significantly slower compared to placebo in the first half of the GE curve (25%-50% fractional GE).

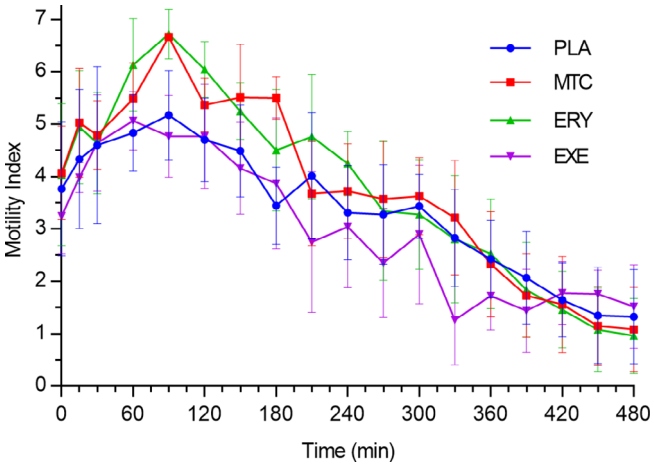

FIGURE 2 Motility index curves generated by graphing the mean ± SD of the MI (product of antral contraction amplitude and contraction frequency) over time after placebo and each drug (metoclopramide, erythromycin, exenatide) in 8 healthy domestic shorthair cats

P = .002 – .04; 35% fractional GE, *P* = .05). The rates of GE after administration of erythromycin were significantly faster than after placebo at all fractions of GE (*P* = .001-.02). Although the rate of GE after administration of exenatide appeared slower compared to placebo, the difference was only significant in the first half of the GE curve (25%-50% fractional GE, *P* = .01-.03; 55%-90% fractional GE, *P* = .05-.3).

The time course of the MI of antral contractions is shown in Figure 2. A double peak pattern was observed after administration of each drug. When compared to placebo (1555 ± 286), the significantly larger total AUC of the MI curves after administration of erythromycin (1857 ± 415, *P* = .03) and metoclopramide (1847 ± 253, *P* = .04) indicates an increase in antral motility. The MI was significantly higher at 90 (*P* = .001) and 180 minutes (*P* = .001) after metoclopramide administration and at 60 (*P* < .001), 90 (*P* < .001) and 120 minutes (*P* = .01) after erythromycin. Although the MI was lower at 330 minutes (*P* = .04) after exenatide administration, a significant difference was not found between the total AUC of the MI curves for exenatide (1509 ± 296, *P* = .97) and placebo.

The CA after metoclopramide was significantly higher than CA after administration of placebo at 180 minutes (*P* = .01) after test meal ingestion. Similarly, the CA after erythromycin was significantly higher than the CA after administration of placebo at 60 (*P* = .01), 90 (*P* = .04), and 180 minutes (*P* = .02) after test meal ingestion. The total AUC of CA after administration of metoclopramide (225 ± 17) and erythromycin (222 ± 18) was not significantly larger (*P* = .92, 1.0, respectively) than the total AUC of CA after placebo (221 ± 9). The CA after exenatide was significantly lower than CA after administration of placebo at 360 minutes (*P* = .02) after test meal ingestion, and the total AUC of CA after administration of placebo was significantly larger (*P* = .02) than the total AUC of CA after exenatide administration (202 ± 21).

Finally, metoclopramide and erythromycin administration was associated with a higher CF than placebo at 90 (*P* = .03), 150 (*P* = .03), and 180 minutes (*P* = .03) and 90 (*P* = .03), 120 (*P* = .02), and 150 minutes

(P = .03), respectively. Although the AUC of CF in cats receiving metoclopramide (3908 ± 533, P = .11) and erythromycin (3950 ± 753, P = .06) appeared larger than when they were given placebo (3566 ± 714), the difference was not significant. The antral CF after exenatide was significantly lower than after placebo at 330 minutes (P = .02), but the total AUC of CF after exenatide administration (3472 ± 720, P = .91) was not significantly different from the total AUC of CF after placebo.

4 | DISCUSSION

We compared the effects of metoclopramide, erythromycin, and exenatide on GE and gastric motility to placebo. To the best of our knowledge, this is the first time the effects of these drugs on GE and gastric motility have been evaluated in nonanesthetized cats. The results indicate that both metoclopramide and erythromycin have gastric prokinetic effects, because they shorten GE times and increase the MI of postprandial antral contractions in healthy cats, whereas exenatide causes an initial delay in GE.

Gastric prokinetic drugs play an important role in the management of nonobstructive gastric motility disorders. When effective, gastric prokinetic drugs stimulate contractions in the gastropyloroduodenal area and accelerate GE. Previous research using bethanechol chloride has shown that stimulation of contractions alone is not enough to accelerate GE.[19] Bethanechol stimulates gastric contractions but has no significant effect on the rate of GE.[19,20] An effective gastric prokinetic drug must also stimulate other variables that influence GE, for example, the percentage of contractions that propagate in the stomach, the percentage of contractions that propagate from the antrum or pylorus to the duodenum, the percentage of contractions that propagate in the duodenum, or some combination of these.[19,21] The efficacy of prokinetic drugs in a given patient with delayed GE depends on that patient's underlying problem or dysfunction and the specific variables of gastropyloroduodenal contractions that the prokinetic drug influences.[19,21]

Our results indicate that metoclopramide has a prokinetic effect in the stomach of healthy cats, because it shortens GE times and increases the MI of postprandial antral contractions. Most of the prokinetic effects of metoclopramide are a consequence of its affinity for the 5-hydroxytryptamine type 4 (5HT4) receptor and to lesser degree antagonism at the 5-hydroxytryptamine type 3 (5HT3) receptor.[7,19] Metoclopramide also is an antagonist of dopamine type 2 (D2) receptors that are known to exist in the feline stomach and produce abnormal electrical activity.[22] In dogs that have undergone abdominal surgery, metoclopramide stimulated antral and proximal small intestinal myoelectric and contractile activity, and therefore may be beneficial in the treatment of postoperative ileus in dogs.[23] In normal dogs, however, GE time was not significantly shortened by metoclopramide and the drug mainly enhanced antropyloroduodenal coordination.[21] Although metoclopramide administration increased the sonographic MI of antral contractions in our study, the CA and contraction frequency were not significantly different from placebo. We hypothesize that the increase of sonographic MI was caused by proportional increases in both CA and CF.

In our study, the shortening of GE times and increase in the MI of postprandial antral contractions after administration of erythromycin indicate that this drug has gastric prokinetic effects in healthy cats. Erythromycin is a motilin agonist that at low, antimicrobially ineffective, doses accelerates GE by inducing antral contractions similar to those associated with phase III of the MMC in the interdigestive period.[19] Cats do not appear to display this classic type of interdigestive motility pattern but functional motilin receptors and a motilin precursor have been identified in the feline GI tract, with highest concentrations in the duodenum and lowest concentration in the colon.[7,24-26] In people, it is thought that the gastric prokinetic effects of erythromycin include increased motility of the antrum,[27,28] increased proximal gastric tone,[29] and increased coordination between antral and duodenal contractions.[27,28] In a study characterizing the pharmacokinetic profiles of different erythromycin formulations administered to cats by IV, IM, and PO routes, the plasma concentrations after IV or PO erythromycin were insufficient and led to potential inefficacy. The discrepancy between low plasma concentrations and described clinical effect could be explained by the ability of erythromycin to concentrate in tissues having high tissue/plasma concentration ratios with favorable clinical outcomes.[30] Erythromycin increased the sonographic MI of antral contractions in our study, but as was seen with metoclopramide, the CA and CF were not significantly different when compared to placebo. Thus, we hypothesize that the increase of sonographic MI was caused by proportional increases of both CA and CF.

Our results indicate that exenatide causes an initial delay of GE. The GE times during the second half of the GE curve and the total emptying time were not different from the placebo. Treatment with GLP-1 agonists is gaining popularity in the management of T2DM in people and these drugs also have potential utility in the management of obesity. Previous studies in people found that the administration of GLP-1 inhibited GE.[31-34] Additionally, exenatide has been shown to slow GE in healthy subjects[35] and people with T2DM.[36] The rate of GE is an important determinant of glycemic control in both healthy individuals and those with diabetes (DM).[37-39] The most common form of DM in cats has many similarities with T2DM in people and often is associated with obesity, the most common nutritional disorder in cats.[40] Through effects comparable to those observed in people, exenatide could prove beneficial in the treatment of DM and obesity in cats. In general, exenatide is well tolerated in people and cats, but mild adverse GI effects have been reported.[12-16,41,42] In people, SC GLP-1 administration has been shown to delay the initial phase of GE,[43] cause a dose-dependent delay in GE by prolonging the lag period and to suppress antroduodenal motor activity.[44] This delay in GE did not affect the maximal emptying rate or the total emptying time.[43] In people, exogenous GLP-1 relaxes the proximal stomach in a dose-dependent manner,[45] decreases antral and duodenal motility, and increases pyloric tone in both the fasted and fed states.[12,46] Although we found no significant difference in MI when comparing administration of exenatide to placebo, antral contractions were of lower amplitude in cats receiving exenatide. In addition, exenatide caused a significant prolongation of

the sonographic lag period (significantly longer time to achieve maximal antral dilatation) in our study. The delay between food ingestion and maximal antral dilatation can be explained by slow intragastric distribution of the ingested food because of decreased proximal gastric tone. Although the physiological processes mediating the time required to reach sonographic maximal antral dilatation are not fully understood, the clinical relevance of changes in that time is worthy of further study.[47]

No adverse effects were observed in association with the administered drugs. Cats that received exenatide subjectively had decreased appetite, but the time required for test meal consumption was not statistically different from that after other drugs.

Limitations of our study include small sample size and lack of histologic evaluation of the GI tract to rule out subclinical gastric disease. The cats had no history of GI disease, and the physical examination, laboratory tests and abdominal ultrasound examination did not identify any clinically relevant abnormalities. In the unlikely event that a cat did have subclinical gastropathy, the crossover study design ensured that each cat served as its own control. Blood glucose concentration was not monitored after exenatide administration. Stress associated with handling and restraint was not a limitation of this study because the cats were acclimatized. However, it will need to be taken into consideration in future studies using client-owned cats that are not acclimatized to the necessary handling and restraint. Larger studies evaluating the efficacy of these drugs in client-owned cats with gastric disease are needed.

In conclusion, our results indicate that metoclopramide and erythromycin have gastric prokinetic effects in healthy cats, whereas the administration of exenatide was associated with an initial delay in GE. Additional studies are needed to evaluate the effects of these GI prokinetic drugs and exenatide in cats with GI disease and those with DM and obesity, respectively.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Erythromycin was used as a GI prokinetic at a dose 10-20 times below the recommended for antimicrobial dose.

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

All animal use was approved by the Louisiana State University IACUC and the experiment was performed in an Association for Assessment and Accreditation of Laboratory Animal Care International accredited facility.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Mangel AW, Stavorski JR, Pendleton RG. Effects of bethanechol, metoclopramide, and domperidone on antral contractions in cats and dogs. *Digestion*. 1983;28:205-209.
2. Hogan PM, Aronson E. Effect of sedation on transit time of feline gastrointestinal contrast studies. *Vet Radiol Ultrasound*. 1988;29:85-88.
3. Roche M, Descroix-Vagne M, Benouali S, et al. Effect of some gastrointestinal hormones on motor and electrical activity of the digestive tract in the conscious cat. *Br J Nutr*. 1993;69:371-384.
4. Goggin JM, Hoskinson JJ, Butine MD, Foster LA, Myers NC. Scintigraphic assessment of gastric emptying of canned and dry diets in healthy cats. *Am J Vet Res*. 1998;59:388-392.
5. Peachey SE, Dawson JM, Harper EJ. Gastrointestinal transit times in young and old cats. *Comp Biochem Physiol A Mol Integr Physiol*. 2000;126:85-90.
6. Camilleri M. Gastric motility and gastric emptying. In: Podolsky DK, Camilleri M, Fitz JG, Kalloo AN, Shanahan F, Wang TC, eds. *Yamada's Textbook of Gastroenterology*. 6th ed.Chichester, UK: Wiley-Blackwell; 2016:348-366.
7. Gaschen FP. Disorders of esophageal, gastric, and intestinal motility in cats. In: Little SE, ed. *August's Consultations in Feline Internal Medicine*. 7th ed.St. Louis, MO: Elsevier; 2016:117-128.
8. Itoh Z, Nakaya M, Suzuki T, Arai H, Wakabayashi K. Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. *Am J Physiol*. 1984;247:G688-G694.
9. Itoh Z, Suzuki T, Nakaya M, Inoue M, Mitsuhashi S. Gastrointestinal motor-stimulating activity of macrolide antibiotics and analysis of their side effects on the canine gut. *Antimicrob Agents Chemother*. 1984;26:863-869.
10. Sarna SK, Gonzalez A, Ryan RP. Enteric locus of action of prokinetics: ABT-229, motilin, and erythromycin. *Am J Physiol Gastrointest Liver Physiol*. 2000;278:G744-G752.
11. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132:2131-2157.
12. Marathe CS, Rayner CK, Jones KL, et al. Effects of GLP-1 and incretin-based therapies on gastrointestinal motor function. *Exp Diabetes Res*. 2011;2011:279530.
13. Gilor C, Graves TK, Gilor S, Ridge TK, Rick M. The GLP-1 mimetic exenatide potentiates insulin secretion in healthy cats. *Domest Anim Endocrinol*. 2011;41:42-49.
14. Rudinsky AJ, Adin CA, Borin-Crivellenti S, Rajala-Schultz P, Hall MJ, Gilor C. Pharmacology of the glucagon-like peptide-1 analog exenatide extended-release in healthy cats. *Domest Anim Endocrinol*. 2015;51:78-85.
15. Riederer A, Zini E, Salesov E, et al. Effect of the glucagon-like peptide-1 analogue exenatide extended release in cats with newly diagnosed diabetes mellitus. *J Vet Intern Med*. 2016;30:92-100.
16. Padrutt I, Lutz TA, Reusch CE, Zini E. Effects of the glucagon-like peptide-1(GLP-1) analogues exenatide, exenatide extended-release, and of the dipeptidylpeptidase-4 (DPP-4) inhibitor sitagliptin on glucose metabolism in healthy cats. *Res Vet Sci*. 2015;99:23-29.
17. Husnik R, Fletcher JM, Gaschen L, Gaschen FP. Validation of ultrasonography for assessment of gastric emptying time in healthy cats by radionuclide scintigraphy. *J Vet Intern Med*. 2017;31:394-401.
18. Laflamme DP. Development and validation of a body condition score system for cats: a clinical tool. *Feline Practice*. 1997;25:13-17.
19. Hall JA, Washabau RJ. Diagnosis and treatment of gastric motility disorders. *Vet Clin North Am Small Anim Pract*. 1999;29:377-395.
20. McCallum RW, Fink SM, Lerner E, et al. Effects of metoclopramide and bethanechol on delayed gastric emptying present in gastroesophageal reflux patients. *Gastroenterology*. 1983;84:1573-1577.

21. Orihata M, Sarna SK. Contractile mechanisms of action of gastroprokinetic agents: cisapride, metoclopramide, and domperidone. *Am J Physiol*. 1994;266:G665-G676.
22. Jo YH, Sim SS, Choi H, Kim MS. Effect of dopamine on electrical activity of isolated stomach muscle in cats. *Dig Dis Sci*. 1989;34:548-552.
23. Graves GM, Becht JL, Rawlings CA. Metoclopramide reversal of decreased gastrointestinal myoelectric and contractile activity in a model of canine postoperative ileus. *Vet Surg*. 1989;18:27-33.
24. Greenwood B, Dieckman D, Kirst HA, Gidda JS. Effects of Ly267108, an erythromycin analog derivative, on lower esophageal sphincter function in the cat. *Gastroenterology*. 1994;106:624-628.
25. Xu L, Depoortere I, Thielemans L, Huang Z, Tang M, Peeters TL. Sequence, distribution and quantification of the motilin precursor in the cat. *Peptides*. 2003;24:1387-1395.
26. Depoortere I, Peeters TL, Vantrappen G. Distribution and characterization of motilin receptors in the cat. *Peptides*. 1993;14:1153-1157.
27. Annese V, Janssens J, Vantrappen G, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. *Gastroenterology*. 1992;102:823-828.
28. Tack J, Janssens J, Vantrappen G, et al. Effect of erythromycin on gastric motility in controls and in diabetic gastroparesis. *Gastroenterology*. 1992;103:72-79.
29. Bruley des Varannes S, Parys V, Ropert A, et al. Erythromycin enhances fasting and postprandial proximal gastric tone in humans. *Gastroenterology*. 1995;109:32-39.
30. Albarellos GA, Montoya L, Landoni MF. Pharmacokinetics of erythromycin after intravenous, intramuscular and oral administration to cats. *Vet J*. 2011;187:129-132.
31. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet*. 2002;359:824-830.
32. Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci*. 1993;38:665-673.
33. Naslund E, Bogefors J, Gryback P, et al. GLP-1 inhibits gastric emptying of water but does not influence plasma. *Scand J Gastroenterol*. 2001;36:156-162.
34. Naslund E, Bogefors J, Skogar S, et al. GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. *Am J Physiol*. 1999;277:R910-R916.
35. Edwards CM, Stanley SA, Davis R, et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab*. 2001;281:E155-E161.
36. Kolterman O, Buse J, Fineman M, et al. Synthetic exendin-4 (Exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metabol*. 2003;88:3082-3089.
37. Horowitz M, Edelbroek M, Wishart J, et al. Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. *Diabetologia*. 1993;36:857-862.
38. Mourot J, Thouvenot P, Couet C, Antoine JM, Krobicka A, Debry G. Relationship between the rate of gastric emptying and glucose and insulin responses to starchy foods in young healthy adults. *Am J Clin Nutr*. 1988;48:1035-1040.
39. Horowitz M, O'Donovan D, Jones K, et al. Gastric emptying in diabetes: clinical significance and treatment. *Diabet Med*. 2002;19:177-194.
40. German AJ. The growing problem of obesity in dogs and cats. *J Nutr*. 2006;136:1940S-1946S.
41. Naslund E, Gutniak M, Skogar S, et al. Glucagon-like peptide 1 increases the period of postprandial satiety and slows gastric emptying in obese men. *Am J Clin Nutr*. 1998;68:525-530.
42. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.
43. Schirra J, Leicht P, Hildebrand P, et al. Mechanisms of the antidiabetic action of subcutaneous glucagon-like peptide-1(7–36)amide in non-insulin dependent diabetes mellitus. *J Endocrinol*. 1998;156:177-186.
44. Schirra J, Kuwert P, Wank U, et al. Differential effects of subcutaneous GLP-1 on gastric emptying, antroduodenal motility, and pancreatic function in men. *Proc Assoc Am Physicians*. 1997;109:84-97.
45. Schirra J, Wank U, Arnold R, Göke B, Katschinski M. Effects of glucagon-like peptide-1(7-36)amide on motility and sensation of the proximal stomach in humans. *Gut*. 2002;50:341-348.
46. Schirra J, Houck P, Wank U, Arnold R, Göke B, Katschinski M. Effects of glucagon-like peptide-1(7-36)amide on antro-pyloro-duodenal motility in the interdigestive state and with duodenal lipid perfusion in humans. *Gut*. 2000;46:622-631.
47. Chalmers AF, Kirton R, Wyse CA, et al. Ultrasonographic assessment of the rate of solid-phase gastric emptying in dogs. *Vet Rec*. 2005;157:649-652.

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