High-resolution manometric evaluation of the effects of cisapride and metoclopramide hydrochloride administered orally on lower esophageal sphincter pressure in awake dogs

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Objective—To evaluate the effects of cisapride and metoclopramide hydrochloride administered orally on the lower esophageal sphincter (LES) resting pressure in awake healthy dogs.

Animals—6 adult Beagles.

Procedures—Each dog was evaluated after administration of a single dose of cisapride (0.5 mg/kg), metoclopramide (0.5 mg/kg), or placebo (empty gelatin-free capsule) in 3 experiments performed at 3-week intervals. To measure LES pressure, a high-resolution manometry catheter equipped with 40 pressure sensors spaced 10 mm apart was used. For each experiment, LES pressure was recorded during a 20-minute period with a virtual electronic sleeve emulation before treatment (baseline) and at 1, 4, and 7 hours after drug or placebo administration. A linear mixed-effects model was used to test whether the 3 treatments affected LES pressure differently.

Results—in the cisapride, metoclopramide, and placebo experiments, median baseline LES pressures were 29.1, 30.5, and 29.0 mm Hg, respectively. For the cisapride, metoclopramide, and placebo treatments, median LES pressures at 1 hour after administration were 44.4, 37.8, and 36.6 mm Hg, respectively. For the cisapride, metoclopramide, and placebo treatments, median LES pressures at 7 hours after administration were 44.3, 28.5, and 33.3 mm Hg, respectively. The LES pressures differed significantly only between the placebo and cisapride treatments.

Conclusions and Clinical Relevance—Results suggested that orally administered cisapride may be of benefit in canine patients for which an increase in LES pressure is desirable, whereas orally administered metoclopramide did not affect LES resting pressures in dogs. (Am J Vet Res 2014;75:361–366)

Cisapride and metoclopramide hydrochloride are both drugs commonly used in the treatment of esophageal reflux, esophagitis, and suspected upper gastrointestinal tract motility disorders. Cisapride (a substituted benzamide) is chemically related to metoclopramide but is devoid of central or antidopaminergic properties. It is a 5-hydroxytryptamine (5-HT₄) receptor agonist, and its mode of action is thought to be attributable to an increase in acetylcholine release at the myenteric plexus. Metoclopramide (also a benzamide) acts as a dopamine and 5-HT₁ receptor antagonist and as a 5-HT₄ receptor agonist. Both drugs are thought to increase LES pressure. Therefore, administration of cisapride or metoclopramide in combination with gastric acid suppressants is the recommended treatment for prevention of gastroesophageal reflux. Cisapride or metoclopramide is further recommended in the treatment of esophagitis because it has been shown that esophageal inflammation in itself may cause esophageal hypomotility. In cats, experimentally induced esophagitis decreases esophageal peristalsis, reduces LES pressure, and diminishes esophageal clearance. These changes are reversible with healing of the esophagus. Therefore, patients with any evidence of esophagitis might benefit from treatment with medications that strengthen the LES, thereby preventing further injury and allowing esophageal healing. Two studies revealed a reduction of reflux events in anesthetized dogs after the administration of esomeprazole and cisapride or
metoclopramide. Because LES pressure measurements were not performed in those studies, it remains unclear whether the reduction of reflux episodes was caused by an increase in LES tone, by accelerated gastric emptying due to the drugs’ prokinetic effects, or by a combination of both. Published reports of studies that validate the concept that cisapride and metoclopramide cause an increase in the LES pressure are lacking in veterinary medicine. Notably, the effects of cisapride or metoclopramide over time in awake (nonsedated) or anesthetized dogs have never been investigated. To our knowledge, an increase in LES pressure after cisapride administration has only been shown in 1 study in which dogs were fed immediately before pressure measurement. It is possible that simultaneous ingestion of caloric food might have increased the LES pressure; thus, an overlap between a potential drug effect and a postprandial increase in pressure should be considered.

High-resolution manometry enables a noninvasive evaluation of esophageal sphincter pressures. High-resolution manometry is a new promising diagnostic tool for providing esophageal pressure profiles for dogs without the need of chemical restraint. The closely spaced pressure sensors of manometric catheters enable accurate recording of LES pressure over time, without loss of the LES high-pressure zone due to breathing-, moving-, or swallowing-related change of position. Because the entire esophagus, including the upper esophageal sphincter, tubular esophagus, and LES, is displayed in real time on a screen (Figure 1), deglutitive sphincter relaxation as well as transient LES relaxations can be excluded from LES resting pressure analysis. This enables specific measurement of the LES resting pressure. Therefore, the purpose of the study reported here was to evaluate the effects of oral administration of cisapride and metoclopramide on the LES resting pressure over time in awake healthy dogs by use of HRM.

Materials and Methods

Animals—Six healthy Beagles (median age, 21 months; median body weight, 13.5 kg; and median body condition score, 5/9) were used in the study. Among the dogs, there were 4 females and 2 males. The study was approved by the Cantonal Veterinary Office of Zürich and conducted in accordance with guidelines established by the Animal Welfare Act of Switzerland (permission No. 185/2011).

Experimental procedures—Each dog was evaluated by use of HRM before and after administration of cisapride (0.5 mg/kg [tablet]), metoclopramide hydrochloride (0.5 mg/kg [tablet]), or placebo (empty gelatin-free capsule) in 3 experiments performed at 3-week intervals. Each dog was given 5 mL of water directly in the mouth with a syringe immediately after the drug or placebo was administered. To ensure swallowing of the tablets or the capsule, the dog’s oral cavity was then examined. Experiments involving the placebo were performed first, followed by experiments involv-
ing cisapride and then experiments involving metoclopramide. Personnel were not blinded to the different drug administrations. Prior to each experiment, food but not water was withheld from each dog.

**HRM procedure**—A solid-state catheterd (outer diameter, 3.3 mm) with 40 pressure sensors spaced 10 mm apart was used in each experiment. Prior to each procedure, the catheter was calibrated at 0 mm Hg (atmospheric pressure) and 100 mm Hg (high value), according to the manufacturer's guidelines. Before calibration, the catheter was warmed by immersion in a water bath at 38.0° to 39.0°C for 30 seconds. The depth of the water bath was 1 cm to avoid strong pressure influences due to the water height (1 cm H$_2$O; 0.74 mm Hg). This warming maneuver was performed immediately before each intubation to prevent temperature-sensitive pressure fluctuations (ie, during movement from room temperature environment into warm body environment). Each procedure was performed with the dog in a sitting position. The catheter was lubricated with a 2% lidocaine gel and carefully inserted into the dog’s nose and through the nasopharynx into the esophagus. In this location, an HRM recording of the entire esophagus can be attained, spanning from the hypopharynx to the stomach. Real-time pressure imaging enabled accurate placement of the catheter. Three to 4 pressure sensors were positioned intragastrically to rule out any artifacts caused by breathing-related movements of the esophagogastric junction. During the examination, the inserted catheter was manually held in position. After a 5-minute adaptation time, the LES pressure was recorded during a 20-minute period. Each procedure was performed by the same examiner (JK). Also, during each examination, the same technician sat behind the dog and held it gently in the sitting position. Thus, major movements of the head or changes in position could be prevented during all experiments.

**HRM data**—In each experiment, HRM data were obtained by use of the same protocol before (baseline) and at 1, 4, and 7 hours after cisapride, metoclopramide, or placebo treatment. Manometric data were analyzed with software. The LES pressure was calculated with a virtual electronic sleeve emulation. This type of analysis provides a sleeve calculation over selected pressure sensors spanned by the marker. For each channel for a given point of time, the values are compared across all the channels that the marker is spanning, and the maximum value is then reported as the sleeve value for the given temporal point. All spontaneous deglutitive LES relaxations and the contractions immediately following them displayed on screen were excluded from the analysis (Figure 2). For each time point in a given experiment, the mean of all pressure values was calculated. For each treatment group at each time point, the

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Figure 2—Topographic display of physiologic swallow pressure recorded prior to treatment in 1 of 6 adult Beagles used to evaluate the effects of cisapride and metoclopramide hydrochloride administered orally on the LES resting pressure. Examination was performed with a 40-channel solid-state probe with 10-mm spacing between adjacent pressure sensors. The procedure was performed with the dog in a sitting position. The catheter was lubricated with a 2% lidocaine gel and carefully inserted into the dog’s nose and through the nasopharynx to the stomach. Real-time pressure imaging enabled accurate placement of the catheter. Three to 4 pressure sensors were positioned intragastrically to rule out any artifacts caused by breathing-related movements of the esophagogastric junction. During the examination, the inserted catheter was manually held in position. After a 5-minute adaptation time, the LES pressure was recorded during a 20-minute period. Each procedure was performed by the same examiner (JK). Also, during each examination, the same technician sat behind the dog and held it gently in the sitting position. Thus, major movements of the head or changes in position could be prevented during all experiments.

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median and range for all dogs were calculated. All data were analyzed by the same person.

Statistical analysis—The study objective was to determine whether LES pressure in dogs differed following single-dose treatment with cisapride, metoclopramide, or placebo. Specifically, we used the 3 post-treatment animal-level replicates (at 1, 4, and 7 hours) to determine the differences in LES pressure from baseline (0 hours) across the 3 treatments for each dog. This provided 3 observations for each dog for each treatment. The statistical hypothesis tested was whether the mean difference from baseline differed among the 3 treatments. Owing to the repeated measurements obtained from each dog for each treatment, it was necessary to adjust for correlation between observations. The standard statistical technique for such an adjustment was used, specifically a linear mixed-effects model with animal as a random effect and treatment as a fixed effect. The Holm method was used to correct for multiple comparisons, and this approach provides an adjusted P value for each comparison. Adjusted P values < 0.05 were considered significant.

Results

Animals—Throughout the study, all 6 dogs tolerated insertion of the catheter without chemical restraint at all time points. No adverse effects of treatment or complications secondary to the HRM procedure were evident.

HRM data—Because all spontaneous deglutitive LES relaxations and the contractions immediately following them displayed on screen during the 20-minute examination period were excluded from the analysis, the final assessment of the LES pressure was calculated over a median period of 10.6 minutes for the cisapride experiments, 10.7 minutes for the metoclopramide experiments, and 12.3 minutes for the placebo experiments.

In the cisapride experiments, median pressures were 29.1 mm Hg (range, 23.6 to 48.4 mm Hg) at baseline, 44.4 mm Hg (range, 38.6 to 77.3 mm Hg) at 1 hour after drug administration, 50.7 mm Hg (range, 44.9 to 72.8 mm Hg) at 4 hours after drug administration, and 44.3 mm Hg (range, 43.1 to 54.9 mm Hg) at 7 hours after drug administration. In the metoclopramide experiments, median pressures were 30.5 mm Hg (range, 15.5 to 48.4 mm Hg) at baseline, 37.8 mm Hg (range, 32.9 to 49.5 mm Hg) at 1 hour after drug administration, 30.6 mm Hg (range, 24.0 to 48.0 mm Hg) at 4 hours after drug administration, and 28.3 mm Hg (range, 13.0 to 48.3 mm Hg) at 7 hours after drug administration. In the placebo experiments, median pressures were 29.0 mm Hg (range, 23.2 to 44.6 mm Hg) at baseline, 36.6 mm Hg (range, 32.2 to 55.8 mm Hg) at 1 hour after drug administration, 31.1 mm Hg (range, 13.7 to 44.7 mm Hg) at 4 hours after drug administration, and 33.3 mm Hg (range, 20.9 to 43.7 mm Hg) at 7 hours after drug administration.

The mean difference from baseline across all dogs in the placebo experiments was 3.9 mm Hg. The difference from baseline across all dogs in the placebo experiments and the difference from baseline across all dogs in the cisapride experiments differed (P < 0.001) by 12.7 mm Hg. The difference from baseline across all dogs in the placebo experiments and the difference from baseline across all dogs in the metoclopramide experiments differed (P = 0.446) by −2.9 mm Hg.

Discussion

To our knowledge, the study reported here is the first in which the effects of cisapride and metoclopramide administered orally at recommended doses on the LES pressure in awake dogs over multiple time points have been evaluated. We chose to study the upper standard doses (0.5 mg/kg [typically administered q 8 h]) recommended for treatment of gastroesophageal reflux, esophagitis, regurgitation, and delayed gastric emptying in dogs. Oral drug administration was investigated because that is the route of administration for treatment on an outpatient basis; IV administration was assumed not to reflect a typical real-life scenario. Recommendations advocating the use of cisapride and metoclopramide for their assumed positive effect on the LES are common in the veterinary medical literature. However, these publications are review articles, which are based on data extrapolated from human medicine, lack original references, or cite 2 studies that had major limitations. The extrapolation from human data and the assumption that the drugs have the same effect on the LES in dogs are problematic because of the difference in anatomic characteristics between the 2 species. Few studies actually test the effect of cisapride and metoclopramide on the LES in dogs. A study frequently used as a reference for the strengthening effect of cisapride on the LES in dogs was designed as an animal model for testing the in vivo effect of cisapride after atropine and nifedipine administration in humans. However, LES pressures were not measured under the sole pharmacological influence of cisapride in that study. Thus, the statement that cisapride increases LES pressure in dogs was merely a hypothesis.

Strombeck et al investigated the gas eructation function of the LES in dogs before and after fundectomy by use of a water-perfused manometric catheter fitted with a dent sleeve and side opening above and below the sleeve. A dent sleeve operates as a long pressure sensor and is typically long enough to span the typical range of sphincter movement in a resting condition. It consists of a thin top membrane that is mounted along the side of the catheter, which enables recording of pressure along the length of the sleeve. Incorporation of the dent sleeve avoided the main disadvantages of conventional manometry (ie, loss of LES pressure due to breathing-, moving-, or swallowing-related change of position of the LES). The authors of that study assessed LES pressure after cisapride or metoclopramide administration before fundectomy and found an LES pressure increase from 45.4 to 61.1 mm Hg (with cisapride treatment) and to 62.2 mm Hg (with metoclopramide treatment). However, the report did not clarify how quickly this pressure increase developed after drug administration or its duration and did not indicate the period of LES pressure recording after drug administration. Also, the dogs had been fed immediately prior to manometry, which may have caused an increase in LES pressure by itself. Furthermore, because the

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Few studies,23,26,28 dogs were sedated or anesthetized to minimize any discomfort of the dogs. Lastly, in no pull-through maneuver) were made in the present study. Or, local anesthesia, use of a small-diameter catheter, and pull-through maneuver of the entire evaluation period.

Published literature is available on the pharmacological effect of metoclopramide on the LES in dogs; however, the duration of effect on the LES cannot be determined from those reports.9,22-26 All those studies9,22-26 differ in regard to the manometric device used, manometric method, duration of the evaluation period, timing of LES pressure measurement after drug administration, and drug doses and routes of administration. Even though metoclopramide-induced LES pressure increases of variable magnitude were documented, the pressure increase was significantly different from baseline only during the first 15 minutes after metoclopramide administration, and the drug was administered IV at doses of 0.5 mg/kg,22 1 mg/kg,23 or 20 mg/Beagle.24 Overall, LES pressure was measured 1 hour after drug administration in only 1 study.23 When assessing previously reported data, the invasive nature (stomach fistulas,22,24 oral insertion, and pull-through maneuver of manometric device in awake dogs25) of some of these studies should also be considered; it has been shown that psychological stress has an influence on manometric results in humans,27 and manometry results in dogs may be similarly affected. For this reason, efforts (ie, local anesthesia, use of a small-diameter catheter, and no pull-through maneuver) were made in the present study to minimize any discomfort of the dogs. Lastly, in a few studies,23,26,28 dogs were sedated or anesthetized when measurements were performed, all of which affect LES pressure.

In the present study, the effects of cisapride and metoclopramide on LES pressure in dogs were assessed over an extended period. High-resolution manometry permitted examination of the entire esophagus, which allowed measurement of the LES resting pressure without swallowing- and belching-associated pressure variations in awake dogs. It would have been ideal to continuously measure the LES pressure over a 24-hour period to detect the duration of drug effect and to examine potential periodic or fluctuating drug effects. However, this technique was not available at our institution and appears not to be feasible in awake dogs.5 On assessment of the placebo experiment results, it appeared that the LES pressure itself has diurnal fluctuation. This seems plausible because the LES functions as a dynamic sphincter muscle; therefore, a consistent tonic pressure is not suspected. For this reason, we chose to include a placebo treatment as well as the cisapride and metoclopramide treatments and to assess LES pressures at various posttreatment time points. In contrast, researchers conducting previous studies9,10,22 in which single measurements after drug administration were obtained did not consider LES diurnal pressure fluctuations.

A limitation of the present study was the small number of dogs, and further studies incorporating a larger group of dogs of different breeds are warranted. Albeit somewhat preliminary, this study was undertaken to assess whether metoclopramide and cisapride had any effect on LES pressure in dogs while overcoming the shortcomings of previous investigations.

Contradictory to common belief, metoclopramide administration resulted in no significant changes in LES pressure, whereas cisapride administration significantly increased LES pressure, compared with the effect of placebo, in the dogs of the present study. Interestingly, the prokinetic effects of metoclopramide on the gastric antrum have also been questioned in a recent study.29 If these data can be extrapolated to dogs with suspected reflux esophagitis, additional benefits from the prokinetic effects of metoclopramide seem questionable. We conclude that in canine patients for which improvements in LES pressure would be considered beneficial, cisapride appears to be a more appropriate drug than metoclopramide.

References

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