Influence of metoclopramide on gastroesophageal reflux in anesthetized dogs

Deborah V. Wilson, BVSc, MS; A. Tom Evans, DVM, MS; Whitney A. Mauer, DVM, PhD

Objective—To determine the effect of 2 doses of metoclopramide on the incidence of gastroesophageal reflux (GER) in anesthetized dogs.

Animals—52 healthy dogs undergoing elective orthopedic surgery.

Procedure—In this prospective clinical study, dogs were evaluated before and during orthopedic surgery. The anesthetic protocol used was standardized to include administration of acepromazine, morphine, thiopental, and isoflurane. Dogs were randomly selected to receive an infusion of saline (0.9% NaCl) solution, a low dose of metoclopramide, or a high dose of metoclopramide before and during anesthesia. Treatment groups were similar with respect to age, body weight, duration of food withholding before surgery, duration of surgery, and dose of thiopental administered. Dogs were positioned in dorsal recumbency during surgery. A sensor-tipped catheter was inserted to measure esophageal pH during anesthesia. We defined GER as a decrease in esophageal pH to < 4 or an increase to > 7.5 that lasted more than 30 seconds.

Results—The high dose of metoclopramide (bolus loading dose of 1.0 mg/kg, IV, followed by continuous infusion at a rate of 1.0 mg/kg/h) was associated with a 54% reduction in relative risk of developing GER. The low dose did not significantly affect the incidence of GER.

Conclusions and Clinical Relevance—Administration of metoclopramide by bolus and constant rate infusion at doses much higher than commonly used will reduce the incidence but not totally prevent GER in anesthetized dogs undergoing orthopedic surgery. (Am J Vet Res 2006;67:26–31)

The GES is considered to be the barrier against reflux of gastric contents into the esophagus, and a decrease in resting pressure of the GES is the major factor in the pathogenesis of GER. Relaxation of the GES is mediated by noncholinergic and nonadrenergic pathways and develops with induction of anesthesia in dogs. Many drugs used during anesthesia, including acepromazine, diazepam, morphine, halothane, isoflurane, xylazine, and atropine, reduce the tone of the GES. Gastroesophageal reflux during anesthesia can lead to pulmonary aspiration and associated morbidity and contributes to development of esophageal dysfunction and esophagitis following anesthesia.

On the basis of gastric volume or pH, between 17% and 60% of people undergoing elective surgeries are considered to be at risk of developing GER and regurgitation. Measurement of esophageal pH is considered the criterion-reference standard when investigating GER in people. Gastroesophageal reflux developed during anesthesia in 5% of healthy people in 1 study and in 8 of 50 (16%) people in another study. Gastroesophageal reflux developed during anesthesia in 47 of 270 (17%) healthy dogs in 1 study and 33 of 60 (55%) dogs in another study. The difference in incidence of GER between these studies is probably attributable to differences in the anesthetic agents used.

Metoclopramide (2-methoxy-5-chloroprocainamide) acts centrally as a dopamine antagonist and antiemetic. It can increase the resting tone of the GES in many species. Administration of metoclopramide can prevent GER in unanesthetized dogs. Metoclopramide has few undesirable effects, including negligible hemodynamic effects, at the doses studied and may have a place in the prevention of GER during anesthesia.

Review of the data leaves questions about the effectiveness of metoclopramide for prevention of GER during anesthesia because prior administration of certain drugs may inhibit the effects of metoclopramide on the GES.

We hypothesized that administration of metoclopramide should be associated with a reduction in the incidence of GER during anesthesia. To identify the effectiveness of metoclopramide for reducing GER during anesthesia in dogs, we conducted a randomized clinical study that used healthy dogs undergoing elective orthopedic surgery. Our objective was to provide clinicians with a measure of the benefits associated with the administration of metoclopramide during anesthesia in a population of canine patients at high risk for developing GER.

Materials and Methods

Animals—The study population consisted of dogs undergoing elective orthopedic surgery of the scapulohumer- al, radiohumeral, femorotibial, and tibiotarsal joints during a 9-month period. Dogs were identified prospectively from the elective surgery schedule. Dogs chronically treated with

GES Gastroesophageal sphincter
GER Gastroesophageal reflux
NNT Number needed to treat
OR Odds ratio
CI Confidence interval
drugs that could affect gastric physiologic function or tone of the GES, with a history of dysphagia, regurgitation, or vomiting; or that received food < 4 hours before the induction of anesthesia were excluded. Dogs that weighed < 4.4 kg or were < 6 months old were also excluded.

Informed consent of each owner was obtained prior to inclusion of a dog in the study. This study was approved by the All University Committee on Animal Use and Care at Michigan State University.

**Experimental procedure**—The study was conducted as a prospective, randomized clinical trial. Drugs and dosages used for preanesthetic medication and induction and maintenance of anesthesia were identical in all dogs. Because the data obtained were objective, study personnel were allowed to know the treatment status of each dog.

Initially, dogs were assigned to receive treatments of saline (0.9% NaCl) solution or a low dose of metoclopramide at the time of entry into the study. Treatments were assigned on the basis of a table constructed by use of a random number generator. Treatments were given after administration of preanesthetic medications and insertion of a catheter into a vein, which was accomplished prior to induction of anesthesia.

Metoclopramide was slowly administered IV as a bolus injection (0.4 mg/kg), followed by continuous infusion at a rate of 0.3 mg/kg/h for the duration of the study period (low dose of metoclopramide). After the first 16 metoclopramide-treated dogs were included in the study, the data were analyzed. On the basis of the lack of a significant effect of metoclopramide, the dosage of metoclopramide was increased (bolus injection, 1.0 mg/kg; continuous infusion at a rate of 1.0 mg/kg/h [high dose]). The study continued with dogs receiving the high dose of metoclopramide or saline solution. This resulted in a combination of historical control dogs and new control dogs, which was deemed appropriate because the study was completed in a relatively short time period and there were no other changes in experimental procedures.

Saline solution was used as the control treatment. It was administered at the same time points and in a volume equivalent to that used for metoclopramide.

**Anesthetic management**—For each dog, food was withheld overnight before surgery. Water was available until the time at which preanesthetic medications were administered. Preanesthetic medication was injected 20 minutes before insertion of a catheter into a vein and induction of anesthesia. Drugs administered to all dogs before anesthesia included acepromazine maleate (0.044 mg/kg, IM) and morphine (0.66 mg/kg, IM); identical dosages were used in all dogs. Vomiting after administration of these agents was recorded.

Anesthesia was induced in all dogs by administration of thiopental in an amount necessary to achieve endotracheal intubation. Dogs were intubated and maintained by administration of isoflurane in oxygen through a semiclosed anesthesia circuit for the duration of surgery. Vaporizer settings varied from 1% to 3%. Dogs were allowed to breathe spontaneously. Monitoring of anesthetic depth and cardiovascular function was routinely performed, and results were recorded at 5-minute intervals. Heart rate was obtained by electrocardiographic analysis. Arterial blood pressure was measured during surgery by use of an automated oscillometric method. No baseline values in awake dogs were obtained. All dogs received an IV infusion of a balanced polyionic solution throughout the duration of the anesthetic period. All dogs were positioned in dorsal recumbency for the duration of surgery. At the completion of the study and before dogs were allowed to recover from anesthesia, postoperative analgesics were administered. Dogs were monitored during recovery for signs of adverse effects (ie, signs of lethargy or extrapyramidal activity).

**Measurement of esophageal pH**—Gastroesophageal reflux was documented by use of a flexible pH sensing probe that was taped to an esophageal stethoscope and inserted into the esophagus. The probe was calibrated (pH 1 and 7) within 2 hours of use. The probe was inserted after induction of anesthesia and endotracheal intubation and removed prior to extubation.

Probe placement was performed by 1 of 3 trained people. To ensure correct and standardized placement of the probe, the distance between the incisor tooth on the lower jaw and the cranial margin of the head of the 10th rib was measured externally. The tip of the probe was then advanced this distance through the oropharynx and into the esophagus, and the probe was affixed in place. This reportedly positions the end of the probe 2 to 7.5 cm oral to the gastroesophageal junction. The probe was then connected to a computer to enable continual data collection for the duration of the anesthetic episode. Data were uploaded at the completion of each study. Analyses of the pH data were performed by use of specific software.

**Vomiting, regurgitation, and GER**—Vomiting was defined in a conscious dog as gastric contents actively deposited on the floor. Regurgitation was defined as passive discharge of liquid from the mouth or nose of a dog during anesthesia. The pH of any fluid that dripped from the mouth or nose was measured. Reflux of gastric contents into the esophagus was defined as 30 seconds or longer of a decrease in esophageal pH to < 4 (reflux of gastric acid) or an increase to > 7.5 (reflux of bile).

**Determination of the study population**—Review of 60 consecutive records of dogs anesthetized in accordance with the anesthetic protocol used in this study and undergoing elective orthopedic surgeries at our veterinary teaching hospital revealed that 33 (55%) dogs had GER during anesthesia. We believe that complete abolition of GER during anesthesia is a desirable but perhaps unattainable goal. Therefore, we considered a reduction in the incidence of GER from the anticipated 55% to 10% would be a meaningful response to treatment with metoclopramide. On the basis of a 1-sided type 1 error protection of 0.05 and power of 0.8, we determined that 17 dogs were needed in each treatment group to detect this reduction in GER.

When determining the practical importance of a research finding, it is useful to evaluate the changes in absolute risk of an event associated with a particular treatment. A good measure of the absolute risk is the NNT. When applied to the study reported here, it was the mean number of anesthetized dogs that a clinician would need to treat with metoclopramide to prevent 1 additional case of GER. To compute the NNT, we used the following equation:

\[
\text{NNT} = \frac{1}{\text{Pc} - \text{Pe}}
\]

where Pc is the incidence of GER in the control group and Pe is the incidence of GER in the experimental (treatment) group.

**Statistical analysis**—Normally distributed data were reported as mean ± SD, whereas data not normally distributed were reported as the median and range. Statistical analyses were performed on a personal computer by use of commercially available software. The main risk factor of interest was administration of metoclopramide. Other confounding risk factors evaluated were signalment (age and weight); vomiting after administration of preanesthetic medications; and duration of anesthesia, surgery; and food withholding. The outcome variable of interest was the development of GER. Interval until onset of GER and the amount of time esophageal pH was < 4 or > 7.5 were also evaluated.
Summary statistics were computed for each of the risk factors of interest. The Spearman correlation coefficient was computed to identify potential areas of multicollinearity between each of the risk factors. Univariable logistic regression was conducted for each of the risk factors to assess the degree of association with GER. Age, body weight, dose of thiopental, duration of food withholding before surgery, duration of surgery and anesthesia, arterial blood pressure, and heart rate were compared among groups by use of a 1-way ANOVA. The Fisher exact 2-tailed test was used to test categoric variables for significant differences among groups.

The initial model contained all risk factors that had an OR with a value of $P \leq 0.2$ for univariable analysis. Two-factor effect modifiers in the initial model included those combinations of risk factors that were expected to have biological relevance. From the initial model, a backward method of variable evaluation was conducted by use of the likelihood ratio statistic to assess inclusion or exclusion of risk factors from the final model.

Results

Animals—Fifty-two dogs were included in the study. There were no significant differences among treatment groups with regard to age, weight, sex distribution, or duration of food withholding before surgery (Table 1). One dog in the high-dose treatment group developed GER during anesthesia and subsequently developed gastric dilation and volvulus after recovery from anesthesia, which was subsequently surgically corrected. No other morbidity or death was associated with the episode of anesthesia or study procedures. No specific evaluation was made of the surgical outcome for each of the dogs.

Vomiting—Vomiting before induction of anesthesia was recorded for 28 (54%) dogs in the study. Incidence of vomiting did not differ significantly among the treatment groups. Vomiting was not a significant ($P = 0.14$) risk factor for the development of subsequent GER (OR, 2.87; 95% CI, 0.71 to 11.65). An increase in the duration of surgery was associated, but not significantly ($P = 0.08$), with an increased risk of developing GER. An increase in the duration of anesthesia was not associated with an increased risk of developing GER (OR, 1.62; 95% CI, 0.87 to 3.04).

GER—Twenty-five dogs had an episode of GER during anesthesia. Signalment did not influence specific outcomes. Twelve of 18 dogs in the saline treatment group had at least 1 episode of GER during the study period. There was a significantly ($P = 0.045$) lower number of dogs in the high-dose treatment group (6 of 18) that had GER during anesthesia (OR, 0.13; 95% CI, 0.02 to 0.69; Table 2). The low dose of metoclopramide was not associated with a lower incidence of GER, compared with the incidence for the saline-treated group.

Each episode of GER recorded in the study was acidic, and the onset of GER tended to be abrupt (Figure 1). Only 1 dog regurgitated gastric contents out of its mouth during anesthesia; that dog was in the low-dose treatment group.

One dog of the control group, 1 dog in the low-dose group, and 2 dogs in the high-dose group had GER extremely early in the anesthetic episode (ie, some time between induction of anesthesia and before insertion of the pH sensing probe). We did not detect difficulty with endotracheal intubation or excessive fluid in the pharynx in these 4 dogs. This early reflux was not significantly associated with metoclopramide treatment status. Mean time between probe placement and onset of reflux was 22 minutes for the saline-treated dogs (Table 2). The onset of reflux appeared to be delayed by administration of metoclopramide, but the variance in the data also increased, so this was not a significant effect.

Dogs with GER during anesthesia had a median of 1 episode of reflux during the study period. There was no significant difference in the lowest pH recorded in each of the groups. Total time during which esophageal pH was $< 4$ did not differ significantly among the treatment groups (Table 2).

Interval from the last meal until induction of anesthesia was 18.2 ± 3.6 hours. This represented a surprisingly long period of food withholding. Within the range of food withholding times for these dogs (11 to 23.5 hours), there was no relationship between duration of food withholding and the incidence of vomiting after administration of preanesthetic medications or GER during the subsequent anesthetic episode.

Anesthetic records were inspected in an attempt to identify an association between the onset of GER and specific events, such as administration of an antimicrobial or the start of surgery. No strong chronologic relationship was apparent. All dogs in the study received an antimicrobial (cephazolin, IV) after induction of anesthesia. In 5 of 25 dogs that had GER, there was an interval of $< 20$ minutes between administration of the antimicrobial and onset of GER, and in 3 of the 25 dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saline</th>
<th>Low*</th>
<th>High†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of dogs</td>
<td>18</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Females (spayed)</td>
<td>1(8)</td>
<td>1(6)</td>
<td>0(8)</td>
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<td>Neutered males</td>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age (y)‡</td>
<td>5.3 ± 2.7</td>
<td>4.8 ± 3.35</td>
<td>5.39 ± 2.64</td>
</tr>
<tr>
<td>Weight (kg)‡</td>
<td>32.3 ± 11.4</td>
<td>33.4 ± 10.8</td>
<td>32.2 ± 10.6</td>
</tr>
<tr>
<td>Food withheld (h)‡</td>
<td>17.4 ± 4.09</td>
<td>19.3 ± 3.9</td>
<td>18 ± 2.6</td>
</tr>
</tbody>
</table>

*The IV administration of a bolus of metoclopramide (0.4 mg/kg) followed by continuous infusion at a rate of 0.3 mg/kg/h. †The IV administration of a bolus of metoclopramide (1.0 mg/kg) followed by continuous infusion at a rate of 1.0 mg/kg/h. ‡Values reported are mean ± SD.
with GER, < 20 minutes elapsed between start of surgery and onset of GER.

Esophageal pH in the dogs that did not have GER varied little throughout the study period (Figure 2). In dogs that did not have GER, mean ± SD esophageal pH was 5.95 ± 0.48 when the probe was first inserted and 5.76 ± 0.62 immediately before the probe was removed.

Cardiovascular data—Initial heart rate, ending heart rate, and mean heart rate during the study period were compared among dogs receiving the 3 treatments (Table 2). Heart rate increased significantly \((P < 0.001)\) from the beginning of the end of the study period, but the effect of treatment was not significant \((P = 0.7)\). Data collection for arterial blood pressure commenced after the surgery site was prepared and the dogs were moved to the surgery table (approx 1 hour after the start of anesthesia). Initial mean blood pressure, ending mean blood pressure, and mean blood pressure throughout the study period were compared (Table 2). Mean arterial blood pressure increased significantly \((P < 0.001)\) from the beginning to the end of the study period, but the effect of treatment was not significant \((P = 0.2)\).

NNT—Treatment with the low or high dose of metoclopramide was associated with a reduction of absolute risk of developing GER (reduction of 23% and 36%, respectively). Relative risk, as compared with results for the saline treatment, was reduced by 34% and 54%, respectively, for the low and high doses. The NNT was 4.4 for the low dose and 2.8 for the high dose of metoclopramide. This indicated that for every 4.4 dogs administered the low dose of metoclopramide (IV administration of a bolus [0.4 mg/kg] followed by continuous infusion at a rate of 0.3 mg/kg/h for the duration of anesthesia), there would be 1 less dog that developed GER. Similarly, for every 2.8 dogs administered the high dose of metoclopramide (IV administration of a bolus [1.0 mg/kg] followed by continuous infusion at a rate of 1.0 mg/kg/h for the duration of anesthesia), there would be 1 less dog that developed GER.

Discussion

The objective of the study reported here was to evaluate the effectiveness of metoclopramide for reducing the incidence of GER in dogs during anesthesia in a clinical setting. The major finding of this study was that the IV administration of metoclopramide as a bolus injection of 1.0 mg/kg followed by a continuous infusion at a rate of 1.0 mg/kg/h reduced the incidence of and risk of developing GER during anesthesia. Metoclopramide administration was not associated with any observable cardiovascular or other adverse effects in the study.

Metoclopramide can increase pressure in the GES of dogs and humans, and it has been used to prevent esophageal reflux of gastric contents.\(^2,21,29\) The effects of metoclopramide on the GES can be reduced by withholding of food and by administration of some antihistaminic and anticholinergic agents.\(^2,21,31,32\)

We elected to include calculations of the reduction in relative risk for developing GER and the NNT that was associated with the 2 doses of metoclopramide. These values allow clinicians to easily apply results of this clinical study.\(^24\) Administration of the high dose of metoclopramide resulted in a 54% reduction in the relative risk of developing GER. Therefore, administration of this dose of metoclopramide during anesthesia would be associated with 1 fewer dog with GER for
every 3 dogs treated. The high incidence of GER during anesthesia in dogs anesthetized by use of the anesthetic protocol provides a good model for assessing the effects of therapeutic interventions on GER, and it is clinically relevant. A crossover study would probably have provided more results that were significant by reducing individual variability, but this was not feasible for our population of dogs.

Administration of metoclopramide increases the tone and amplitude of gastric contractions, relaxes the pyloric sphincter, and increases peristalsis of the duodenum and jejunum.\(^{33,34}\) Classified as an intestinal prokinetic agent, it appears to have less effect on gastric emptying than has been believed.\(^{35}\) Administration of metoclopramide at various dosages can increase tone of the GES.\(^{2,6,29-32}\) Pressure in the GES of fed dogs is maintained by chemicals interacting with cholinergic, histaminic, gastrin, and serotonergic receptors.\(^{31}\)

Metoclopramide administered IV at dosages ranging from 0.2 to 10 mg/kg can increase tone in the GES in awake or anesthetized dogs.\(^{2,5,30-32,35}\) For this range of dosages, there does seem to be a relationship between dose of metoclopramide and magnitude of effect on the GES.\(^{2,5,30-32,35}\) Metoclopramide administered IV as a bolus injection (0.4 mg/kg) to awake dogs caused an increase in GES pressure of 37%\(^{31}\) and 50%,\(^{6}\) respectively. In another study\(^{1}\) in thiopental-anesthetized dogs, IV administration of a bolus dose of 0.2 mg of metoclopramide/kg caused GES pressure to double. After IV administration of a bolus of metoclopramide (1 mg/kg) to thiomebumal-anesthetized dogs, there was an immediate increase in GES pressure of 160% that persisted for 1 hour.\(^{35}\) In pentobarbital-anesthetized dogs, administration of 2 mg of metoclopramide/kg can increase esophageal barrier pressures by 250%.\(^{36}\)

The wide range of doses evaluated made it a challenge to select a dosing strategy for metoclopramide. We started by determining the dosage commonly used for dogs at our veterinary teaching hospital. When the low dose did not reduce the probability of dogs developing GER, it seemed reasonable to select a higher dose for the remainder of the study.

Analysis of available pharmacokinetic and pharmacodynamic data\(^{2,3,5,31}\) supported the effectiveness of the doses evaluated. Pharmacokinetic studies of metoclopramide have been performed in humans, rabbits, and dogs. After IV administration of 5, 10, and 15 mg/kg to dogs, metoclopramide has a large apparent volume of distribution and a mean ± SD half-life of 36.1 ± 4.1 minutes.\(^{35}\) There is pharmacodynamic evidence in dogs that a single bolus dose of metoclopramide has effects on the GES that persist for 30 to 60 minutes.\(^{35}\) On the basis of this information, we elected to use a bolus injection and subsequent continuous infusion of metoclopramide for our study.

Even at higher doses, metoclopramide administration causes little change in cardiovascular function, which is in contrast to the effects for other prokinetic compounds, such as cisapride and domperidone.\(^{7}\) This enhances the safety for use of metoclopramide during anesthesia. Although there have been no adverse effects reported in studies\(^{39,36}\) in which investigators evaluated metoclopramide experimentally, extrapyramidal signs and sedation are potential sequelae to long-term administration of this compound.

Measurement of pH in the caudal portion of the esophageal lumen is the criterion-referenced standard for the detection of GER. Combined reference and sensor (glass) electrodes are superior with respect to response time, drift, and sensitivity than antimony probes with a remote skin-reference electrode.\(^{37}\) The mean pH detected by 2 probes inserted concurrently in the esophagus of humans differed in 3.1% of data points in supine patients\(^{38,39}\); however, the probes recorded similar acid exposure in most of the subjects.\(^{39}\) It is possible that mucosal abutment of the probe tip may cause a false-negative response. When there is mucosal abutment of the probe tip, the pH recorded will still register a decrease but not below the cutoff value.\(^{39}\) The mean starting pH of 5.6 in the dogs of the study reported here was similar to that reported in another study.\(^{40}\)

In our experience, the incidence of esophageal dysfunction or aspiration pneumonia in healthy dogs after an episode of anesthesia for elective orthopedic surgery is extremely low. Despite a high incidence of GER during anesthesia in this population of dogs, few will develop these problems after recovery from anesthesia. There are clearly additional factors involved in the pathophysiologic processes of GER-related disease that are not yet apparent in this population.

In the study reported here, we investigated the effects of administration of metoclopramide on the incidence of GER in healthy dogs undergoing elective orthopedic surgery. The major finding was that IV administration of a high dose of metoclopramide before and during anesthesia caused a significant decrease in the incidence of GER but did not completely prevent it.

### References


