

# Effects of preanesthetic administration of morphine on gastroesophageal reflux and regurgitation during anesthesia in dogs

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**Objective**—To determine the effect of morphine administered prior to anesthesia on the incidence of gastroesophageal reflux (GER) in dogs during the subsequent anesthetic episode.

**Animals**—90 dogs (30 dogs/group).

**Procedure**—The randomized prospective clinical study included healthy dogs with no history of vomiting. Dogs were scheduled to undergo elective orthopedic surgery. Food was withheld for (mean  $\pm$  SD)  $17.8 \pm 4.1$  hours prior to induction of anesthesia. The anesthetic protocol included acepromazine maleate, thiopental, and isoflurane. Dogs were randomly selected to receive morphine at various dosages (0, 0.22, or 1.10 mg/kg, IM) concurrent with acepromazine administration prior to induction of anesthesia. A sensor-tipped catheter was used to measure esophageal pH, and GER was defined as a decrease in pH to  $< 4$  or an increase to  $> 7.5$ .

**Results**—40 dogs had acidic reflux, and 1 had biliary reflux. Proportions of dogs with GER were 8 of 30 (27%), 15 of 30 (50%), and 18 of 30 (60%) for morphine dosages of 0, 0.22, and 1.10 mg/kg, respectively. Mean duration of GER was  $91.4 \pm 56.8$  minutes. There was no significant association between GER and age, weight, vomiting after preanesthetic medication, administration of antimicrobials, or start of surgery.

**Conclusions and Clinical Relevance**—Most healthy dogs vomit after a large dose of morphine, but vomiting does not increase the likelihood of GER during the subsequent anesthetic episode. Administration of morphine prior to anesthesia substantially increases the incidence of GER during the subsequent anesthetic episode. (*Am J Vet Res* 2005;66:386–390)

Clinical studies of gastroesophageal reflux (GER) in humans use measurement of esophageal pH as the criterion-referenced standard for diagnosis of the condition. Reflux of gastric contents into the esophagus is recorded when esophageal pH decreases to  $< 4.0$  (acidic reflux) or increases to  $> 7.5$  (biliary reflux).

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This reflux of gastric contents reportedly was evident during anesthesia in 47 of 270 (17.4%) dogs receiving thiopental and halothane in combination with other agents and in 17 of 34 (50%) dogs receiving propofol.<sup>1-3</sup> An incidence of 5% has been reported<sup>4</sup> for GER in a population of anesthetized people. This reflux is clinically inapparent and usually acidic.<sup>1,5</sup> In some cases, the refluxed fluid is of sufficient volume to reach the pharynx and even drain from the mouth (ie, regurgitation). This material may be aspirated into the lungs leading to pneumonitis<sup>5</sup> or may cause local irritation of the esophagus as a prelude to development of ulcerative esophagitis and stricture formation.<sup>6-8</sup>

Measurement of esophageal pH allows investigation of the incidence and causes of GER during anesthesia. Gastroesophageal reflux happens when the effectiveness of the lower esophageal sphincter is decreased by administration of anesthetic agents, gastric acidity, and withholding of food prior to anesthesia.<sup>4,9,10</sup> Esophageal manometry has also been used to measure esophageal barrier pressures and to investigate effects of some anesthetic agents on these pressures. Lower esophageal sphincter pressure decreases in dogs after administration of drugs, including isoflurane, atropine, acepromazine, and xylazine.<sup>11,12</sup> Meperidine, a narcotic analgesic, actually increases lower esophageal sphincter pressure in dogs but not in cats, humans, or monkeys.<sup>13,14</sup> The effects of other opioids remain to be determined. Monitoring of esophageal pH has a higher degree of sensitivity and specificity for the diagnosis of GER than does manometric or endoscopic examinations.<sup>15</sup>

Morphine is a potent narcotic analgesic that is extremely popular as a preemptive and postoperative analgesic. We hypothesized that preanesthetic administration of morphine would increase the incidence of GER during anesthesia. Our objective was to measure esophageal pH to detect GER in dogs that received morphine at various dosages prior to induction of anesthesia.

## Materials and Methods

**Animals**—Ninety healthy dogs admitted to our veterinary medical teaching hospital for elective surgery of the femorotibial ( $n = 69$  dogs), femoropatellar (14), tarsocrural (6), or cubital (1) joint were included in the study. Mean  $\pm$  SD age of the dogs was  $4.8 \pm 2.4$  years, and they weighed  $32 \pm 12.7$  kg at the time of surgery. Dogs that were receiving long-term treatment with drugs affecting gastric physiologic processes or tone of the lower esophageal sphincter; that had a history of dysphagia, regurgitation, or vomiting; or that had been fed  $< 4$  hours before the induction of anesthesia were excluded. This study was approved by the All University Committee on Animal Use and Care.

**Study protocol**—Food was withheld from all dogs overnight prior to surgery and until recovery from anesthesia. Water was available until the time of administration of preanesthetic medications. Dogs were randomly assigned to receive morphine at various dosages (0, 0.22, or 1.10 mg/kg; each dose was administered to 30 dogs) in combination with acepromazine maleate (0.044 mg/kg), IM, 20 minutes prior to induction of anesthesia. Drugs used for induction and maintenance of anesthesia were identical in all dogs. Anesthesia was induced in all dogs with an amount of thiopental necessary to achieve endotracheal intubation. Dogs were then intubated, and anesthesia was maintained by administration of isoflurane in oxygen through a semiclosed anesthesia circuit for the duration of surgery. Monitoring of anesthetic depth and cardiovascular function was routinely performed.

All dogs were positioned in dorsal recumbency for the duration of surgery. Cephazolin was administered IV to all dogs after induction of anesthesia and every 2 hours subsequently during surgery. Postoperative analgesics were administered at the completion of surgery and prior to recovery from anesthesia.

**Vomiting, regurgitation, and GER**—Vomiting was defined as gastric contents actively deposited on the floor. Vomiting of material after administration of the preanesthetic medicants was recorded. 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. Gastroesophageal reflux was defined as a decrease in esophageal pH to < 4.0 (acidic reflux) or an increase to > 7.5 (biliary reflux).

**Esophageal pH**—Gastroesophageal reflux was documented by introduction of a flexible pH sensing probe<sup>a</sup> into the esophagus. The probe was taped to an esophageal stethoscope and inserted after induction of anesthesia at a time when the dog was judged to be at a sufficiently deep plane of anesthesia to tolerate insertion; the probe was removed prior to extubation. To ensure correct and standard placement of the probe, the distance between the incisor tooth (on the lower hemimandible) and cranial margin of the head of the 10th rib across the angle of the mandible was measured externally. The tip of the probe was then advanced this distance through the oropharynx and into the esophagus and affixed in position. This placement reportedly results in repeatable placement of the end of the probe 2 to 7.5 cm orad to the gastroesophageal junction.<sup>15</sup> The probe was connected to a computer<sup>b</sup> for continual collection of data for the duration of anesthesia. Data were uploaded at the completion of each surgery.

**Statistical analysis**—The main risk factor of interest was administration of morphine (0, 0.22, or 1.10 mg/kg, IM). Other risk factors included were signalment (age and weight); dose of thiopental; and duration of anesthesia, surgery, and withholding of food. Outcome variables of interest were vomiting, regurgitation, or GER. Descriptive statistics were generated for all risk factors on the basis of outcome variables (vomiting, regurgitation, and GER). Age, body weight, dose of thiopental, duration of withholding of food, and duration of anesthesia were compared among groups by use of a 1-way ANOVA.<sup>c</sup> The Fisher exact 2-tailed test was used to test for significant differences in categorical variables among groups. Separate multivariable logistic regression models were created for each outcome to assess the effects of risk factors on outcome, which were reported as **odds ratios (ORs)** with 95% **confidence intervals (CIs)**. All data were reported as mean ± SD, unless stated otherwise. Values of  $P < 0.05$  were considered significant.

## Results

Forty-one of 90 (46%) dogs in the study reported here had an episode of GER during anesthesia. The reflux fluid was acidic in 40 dogs; 1 dog had a brief period of biliary reflux. As the dosage of morphine administered increased from 0 to 0.22 to 1.10 mg/kg, the proportions of dogs that had GER increased from 8 of 30 (27%) to 15 of 30 (50%) to 18 of 30 (60%), respectively (Table 1). The lowest pH recorded in these dogs was 0.1. Age and weight of the dogs did not influence the likelihood of vomiting, GER, or regurgitation during anesthesia. The addition of morphine to the acepromazine significantly ( $P = 0.03$ ) increased the prevalence of GER for the dosage of 0.22 mg/kg (OR, 3.53; 95% CI, 1.09 to 11.44) and 1.10 mg/kg (OR, 3.15; 95% CI, 1.03 to 9.62). Median interval between induction of anesthesia and onset of GER was 10 minutes. In 40 of 41 dogs, there was only 1 episode of GER recorded during the measurement period. The remaining dog had 2 episodes of GER; the first was 35 minutes after induction, and the second was 3 hours after induction. Median duration of an episode of GER was 95 minutes (range, 7 to 200 minutes).

Five of 90 dogs regurgitated during anesthesia. There were 1, 1, and 3 dogs that regurgitated following administration of morphine at dosages of 0, 0.22, and 1.10 mg/kg, respectively. The fluid that dripped from the nose or mouth in these dogs varied from pH 1.4 to 9.0 and was typically colorless, although it was brown in 1 dog. The 5 dogs that regurgitated all had onset of GER between 0 and 16 minutes after placement of the pH probe.

The incidence of vomiting after administration of preanesthetic medications increased significantly ( $P < 0.001$ ) as the dosage of morphine increased. We observed that 0 of 30, 9 of 30 (30%), and 24 of 30 (80%) dogs vomited following IM administration of morphine at 0, 0.22, and 1.10 mg/kg, respectively. The vomitus was usually clear fluid or frothy foam. Of the 33 dogs that vomited after administration of preanes-

Table 1—Vomiting, gastroesophageal reflux (GER), and regurgitation in 90 dogs administered morphine at various dosages (0, 0.22, or 1.10 mg/kg, IM); each dose was administered to 30 dogs) prior to anesthesia.

Event	Morphine (mg/kg)		
	0	0.22	1.10
Vomiting	0	9	24
All cases of GER	8	15	18
GER preceded by vomiting	0	4	14
GER not preceded by vomiting	8	11	4
Regurgitation	1	1	3
Induction to onset of GER (min)*	8 (0–192)	14 (0–110)	10 (0–87)
Duration of GER (min)*	114 (21–149)	88 (7–145)	100 (1–200)
Lowest esophageal pH†	0.1–1.4	0.1–2.1	0.1–2.7

Vomiting was defined as gastric contents actively deposited on the floor. Gastroesophageal reflux was defined as a decrease in esophageal pH to < 4.0 (acidic reflux) or an increase to > 7.5 (biliary reflux). Regurgitation was defined as passive discharge of liquid from the mouth or nose of a dog during anesthesia.

\*Values reported are median (range). †Values reported are the range.

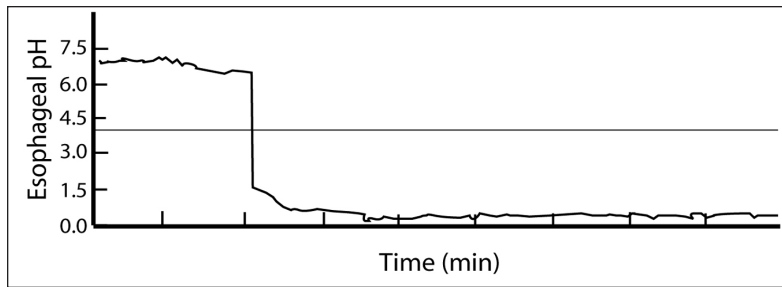


Figure 1—Representative recording of esophageal pH in a dog that had an episode of gastroesophageal reflux (GER) during anesthesia. The threshold used to define an episode of GER was pH 4.0 (horizontal line). The interval between marks on the x-axis is 10 minutes.

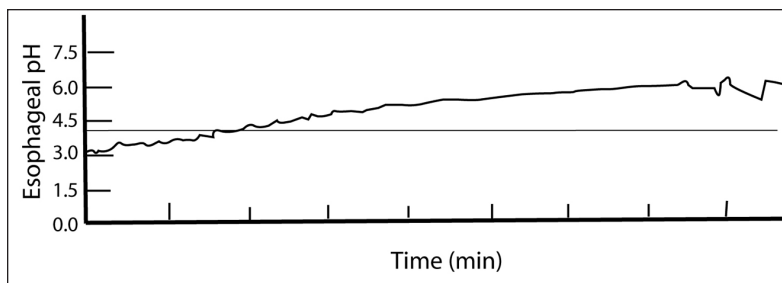


Figure 2—Representative recording of esophageal pH in a dog that had an episode of GER during anesthesia followed by a slow gradual increase in esophageal pH. See Figure 1 for key.

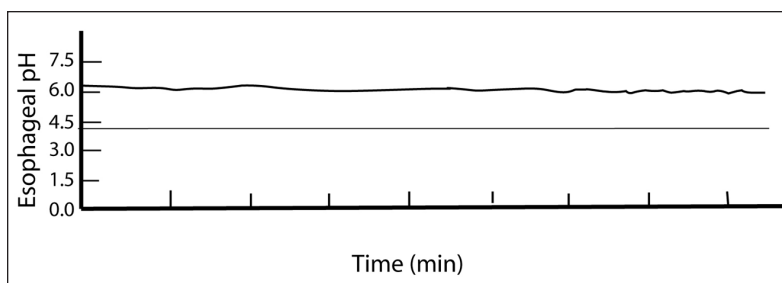


Figure 3—Representative recording of esophageal pH in a dog that did not have GER during anesthesia. See Figure 1 for key.

thetic medications, 17 also had GER during the subsequent anesthetic episode but the remaining 16 did not (Table 1). Twenty-three dogs that had GER during anesthesia did not vomit after administration of preanesthetic medications. There was no relationship between vomiting and subsequent development of GER. Similarly, signalment (age and weight) did not influence the likelihood of vomiting or GER.

In 14 dogs, reflux was evident shortly after induction of anesthesia and prior to probe placement. The incidence of this early GER increased as the dosage of morphine increased (1, 5, and 8 dogs following administration at dosages of 0, 0.22, and 1.10 mg/kg, respectively). Seven of 14 (50%) dogs with early GER vomited after administration of preanesthetic medications, and 7 did not. There was great variability in the amount of time that elapsed from induction to the onset of GER; this ranged up to 192 minutes (mean,  $23 \pm 37.7$  minutes). Esophageal pH abruptly decreased with each GER event (Figure 1). In some dogs, the pH would remain low for the remainder of the measure-

ment period, whereas in others, the pH would then increase to  $> 4.0$  (Figure 2). Esophageal pH remained fairly constant over the study period in the dogs that did not have an episode of GER (Figure 3). Mean esophageal pH at the start of the study was  $6.3 \pm 0.65$  in the dogs that did not have an episode of GER. Esophageal pH remained relatively constant in the nonrefluxing dogs and was  $5.8 \pm 0.57$  at the end of the study. Two dogs that were administered morphine had a starting pH that was  $> 4.5$  but  $< 5.0$ , but it never decreased to  $< 4.0$ .

The interval from the last meal until induction of anesthesia was  $17.8 \pm 4.1$  hours (range, 10 to 30 hours). This represented a prolonged period of food withholding, although dogs did have access to water until the time of administration of preanesthetic medications. Within the range of times included, there was no relationship between duration of food withholding and the incidence of vomiting or GER. Anesthetic records were inspected in an attempt to correlate the onset of GER with specific events, such as administration of an antimicrobial or the start of surgery. In 3 of the 41 dogs that had GER, there was an interval of  $< 20$  minutes that separated the administration of the antimicrobial and onset of GER. In all other dogs that had GER, there was no chronologic relationship between these 2 events. Similarly, 3 dogs had an interval of 5 to 20 minutes that separated the episode of GER and onset of surgery. For all other dogs that had GER, there was an interval of  $> 20$  minutes between these 2 events.

The dosage of thiopental used for induction of anesthesia and intubation was  $11.8 \pm 3.1$ ,  $10.8 \pm 2.7$ , and  $9.4 \pm 2.1$  mg/kg for the 3 dosages of morphine (0, 0.22, and 1.10 mg/kg, respectively). Dosage of thiopental had no significant effect on the risk of developing GER (OR, 0.96; 95% CI, 0.82 to 1.16). Mean duration of anesthesia was  $2.9 \pm 0.9$  hours and did not differ significantly among the 3 groups of dogs. Mean duration of the surgical procedure was  $1.5 \pm 0.6$  hours and did not differ significantly among the 3 groups. An increase in the duration of anesthesia carried a significant increase for the risk of developing GER (OR, 2.67; 95% CI, 1.04 to 6.86). An increase in the duration of surgery was not significantly correlated with the risk for developing GER (OR, 0.24; 95% CI, 0.06 to 1.02).

## Discussion

The large number of patients at our facility that regurgitate during anesthesia piqued our interest in GER. We found that 5 of 90 dogs in the study reported here regurgitated, which is higher than the rates (1 of 240 dogs<sup>1</sup> and 2 of 270 dogs<sup>2</sup>) reported in other stud-

ies. Morphine decreases pressure of the lower esophageal sphincter and increases the probability of reflux in rhesus monkeys and people.<sup>12</sup> Changes in pressure of the lower esophageal sphincter should precede GER but do not predict an episode of GER. Thus, it is important to study esophageal pH.

Another interesting finding of the study reported here was the increase in incidence of vomiting as the dosage of morphine increased. Twenty-four of 30 (80%) dogs receiving the high dose of morphine, IM, vomited, compared with only 9 of 30 (30%) dogs receiving the low dose. The potent emetic effect of morphine when administered at a rate of 1.10 mg/kg, IM, has been reported in another study<sup>16</sup> in which 5 of 6 (83%) dogs vomited after administration at that dosage. The effects of morphine are generally considered to be dose dependent.<sup>14,16</sup> It is possible that vomiting prior to induction of anesthesia would decrease the likelihood of subsequent GER by emptying the stomach or could leave residual acid in the esophagus, but analysis of our data suggests that neither event is obvious or important.

Measurement of pH near the gastroesophageal sphincter is the criterion-referenced standard for detection of GER. A combination of reference and sensor electrodes is superior with respect to response time, drift, and sensitivity, compared with antimony probes with a reference remote skin electrode.<sup>17</sup> The mean pH detected simultaneously by 2 probes in the esophagus of humans differs in 3.1% of supine patients<sup>18,19</sup>; however, the probes record similar acid exposure in most patients.<sup>19</sup> It is possible, but unlikely, that mucosal abutment of the probe tip may cause a false-negative result. When there is mucosal abutment of the probe tip and GER develops, the pH recorded will still register a decrease but not to below the cutoff value.<sup>20</sup> In the study reported here, we found 2 dogs with an esophageal pH > 4.5 but < 5.0. Their inclusion as dogs with GER would not have caused a meaningful change in our interpretation of the data. Certainly, placement of the esophageal stethoscope and probe changed conditions in the esophagus, but all dogs were treated equally in this respect.

The incidence of GER in dogs that did not receive morphine (control group) was 58% higher than the incidence of GER reported in dogs anesthetized by use of a similar protocol in another study<sup>1</sup> (27% in our study vs 17% in the other study). Agents used in the other study were propionylpromazine, thiopental, and halothane. It is interesting to speculate as to the reasons why this large difference exists. One difference between protocols that may serve as an explanation is the use of isoflurane rather than halothane for maintenance of anesthesia. Isoflurane can cause a higher incidence of GER than halothane when administered with nitrous oxide in dogs.<sup>11</sup> Another possible cause of the higher incidence of GER in our study is that acepromazine (0.1 mg/kg, IV) can cause a decrease in gastroesophageal pressure (from 48 to 18 mm Hg) in dogs.<sup>12</sup> Perhaps this effect is more pronounced than the effect of propionylpromazine on lower esophageal sphincter pressure.

The lower esophageal sphincter undergoes phasic contraction and relaxation, and nonpharmacologic factors can contribute to sphincter relaxation and an

episode of GER.<sup>9</sup> The composition of gastric contents influences the incidence of GER,<sup>9,10</sup> and the duration of food withholding prior to anesthesia influences gastroesophageal sphincter pressure.<sup>10</sup> Mean length of the lower esophageal sphincter as measured manometrically in dogs is  $4.6 \pm 0.92$  cm.<sup>15</sup>

Food was withheld from the dogs of our report for a mean of 18 hours prior to induction of anesthesia. This is similar to the duration of withholding of food reported in 2 other studies<sup>1,2</sup> of GER in dogs. Eighteen hours of food withholding can cause a reduction of gastroesophageal sphincter pressure in conscious dogs.<sup>10</sup> Prolonged withholding of food causes an increase in the incidence of GER in dogs.<sup>2</sup> In that same study,<sup>2</sup> investigators reported that none of the dogs had GER when they were fed between 2 and 4 hours prior to induction of anesthesia. Increased gastric acidity can increase the incidence of GER.<sup>10</sup> This relationship between preanesthetic withholding of food and GER during the subsequent anesthetic episode is intriguing and definitely requires additional investigation. The preponderance of acid reflux episodes in the dogs of the study reported here mirrors the findings of 3 other studies<sup>1-3</sup> of GER in anesthetized dogs.

The study reported here provides evidence that the administration of morphine to healthy dogs prior to anesthesia is related to a significant increase in the incidence of GER during the subsequent anesthetic episode. Twenty-four of 30 (80%) dogs administered the high dose of morphine vomited, whereas none of the dogs administered only acepromazine vomited. There appeared to be no relationship between vomiting, the start of surgery, or administration of antimicrobials and development of GER. The clinical importance of these episodes of GER remains to be determined.

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  - b. Digitrapper, Medtronic Functional Diagnostics, Shoreview, Minn.
  - c. SAS information systems for Windows, version 8, SAS Institute Inc, Cary, NC.
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