Influence of halothane, isoflurane, and sevoflurane on gastroesophageal reflux during anesthesia in dogs

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Overview

Objective—To determine whether maintenance of anesthesia with halothane or sevoflurane is associated with a lower incidence of gastroesophageal reflux (GER) than the use of isoflurane in dogs undergoing orthopedic surgery.

Animals—90 dogs.

Procedures—Dogs were evaluated during elective orthopedic surgery. Dogs with a history of vomiting or that had received any drugs that would alter gastrointestinal tract function were excluded from the study. The anesthetic protocol used was standardized to include administration of acepromazine maleate and morphine prior to induction of anesthesia with thiopental. Dogs were allocated to receive halothane, isoflurane, or sevoflurane to maintain anesthesia. A sensor-tipped catheter was placed to measure esophageal pH during anesthesia. Gastroesophageal reflux was defined as an esophageal pH < 4 or > 75.

Results—51 dogs had 1 or more episodes of acidic GER during anesthesia. Reflux was detected in 14 dogs receiving isoflurane, 19 dogs receiving halothane, and 18 dogs receiving sevoflurane. In dogs with GER, mean ± SD time from probe placement to onset of GER was 36 ± 65 minutes and esophageal pH remained < 4 for a mean of 64% of the measurement period. There was no significant association between GER and start of surgery or moving a dog on or off the surgery table. Dogs that developed GER soon after induction of anesthesia were more likely to regurgitate.

Conclusions and Clinical Relevance—Maintenance of anesthesia with one of the 3 commonly used inhalant agents is associated with a similar risk of development of GER in dogs. (Am J Vet Res 2006;67:1821–1825)

Gastroesophageal reflux during anesthesia is usually clinically inapparent. Approximately half the dogs that received preanesthetic administration of morphine subsequently develop GER. In approximately one fourth of the dogs that develop GER, the refluxed gastric contents reach the pharynx (regurgitation) in sufficient quantity to represent a risk for aspiration.

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ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>GER</td>
<td>Gastroesophageal reflux</td>
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<tr>
<td>GESP</td>
<td>Gastroesophageal sphincter pressure</td>
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<tr>
<td>NNT</td>
<td>Number needed to treat</td>
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Regurgitation is also a factor implicated in the development of postanesthetic esophageal dysfunction, an uncommon but serious sequel to anesthesia. The incidence of GER in dogs during anesthesia reportedly varies from 17% to > 50%. Choice of injectable preanesthetic medications and anesthetic agents has an impact on the frequency of GER.

Halothane has been the inhalant anesthetic used in most studies conducted on GESP and anesthetic-related GER. Halothane is no longer manufactured, and its clinical usage has decreased. Effects of the commonly used inhalant anesthetics on GESP or esophageal barrier pressure have been determined. When combined with 66% nitrous oxide, both sevoflurane and enfurane cause a small reduction in esophageal barrier pressure in children. In adult humans, nitrous oxide administered alone or in combination with halothane or enfurane causes a decrease in GESP of 64%, 25%, and 28%, respectively. In dogs, administration of isoflurane and halothane are associated with some reduction in GESP and barrier pressure is reduced by 21%. In pigs receiving 1.5 times the minimum alveolar concentration of halothane, isoflurane, or desflurane, the GESP is reduced to 62%, 37%, and 83% of baseline values, respectively. Analysis of these data suggests that the risk of GER would be higher when animals are anesthetized with isoflurane than with halothane or desflurane.

Two studies of GER in dogs have listed a low incidence of GER (17%) in dogs receiving halothane for maintenance of anesthesia. In another study in which investigators used similar preanesthetic medications and induction agents in dogs, there was a higher incidence of GER (27%) in dogs receiving isoflurane for maintenance of anesthesia. To our knowledge, the effects of sevoflurane on GER have yet to be evaluated.

We hypothesized that administration of sevoflurane or halothane would be associated with a similar risk of developing GER during anesthesia, compared with the risk of developing GER during administration of isoflurane. To identify the effects of these 3 inhalational anesthetic agents on the incidence of GER during anesthesia, we evaluated healthy dogs undergoing elective orthopedic surgery. Our objective was to measure esophageal pH to detect GER in dogs anesthetized with 3 currently available inhalational anesthetic agents.
Materials and Methods

Animals—The study population consisted of 90 dogs undergoing elective orthopedic surgery of the femorotibial (n = 75 dogs), radiohumeral (6), scapulohumeral (4), hip (3), radiocarpal (1), or tibiotarsal (1) joint during a 6-month period. Dogs were identified prospectively from the elective surgery schedule. Dogs were excluded from the study when they had been chronically treated with drugs that could affect gastric physiologic function or tone of the gastroesophageal sphincter; had a history of dysphagia, regurgitation, or vomiting; or had received food < 4 hours before induction of anesthesia. Dogs that weighed < 4.4 kg or were > 6 months old were also excluded.

Experimental procedure—The study was conducted as a prospective, randomized clinical trial. Drugs and dosages used for preanesthetic medication and induction of anesthesia were identical in all dogs. At the time of entry into the study, dogs were allocated to receive isoflurane, halothane, or sevoflurane for maintenance of anesthesia. Study personnel were aware of the drugs administered to each dog.

Anesthetic management—Food was withheld overnight from all dogs 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.

Sedation at the time of catheter placement was scored by 1 of 2 trained evaluators (DVW, DTB) by use of a visual analogue scale (scale of 0 to 10 cm, where 0 = no evidence of sedation and 10 = most sedation imaginable). Thus, a numeric score (the number of centimeters) was recorded.

Anesthesia was induced in all dogs by administration of thiopental in an amount necessary to achieve endotracheal intubation. Dogs were then intubated, and anesthesia was maintained by administration of one of the inhalant agents in oxygen through a semiclosed anesthesia circuit for the duration of surgery. Vaporizer settings varied from 1% to 3% for isoflurane and from 0.5% to 1% for sevoflurane. Dogs were allowed to breathe spontaneously. Monitoring of anesthetic depth and cardiovascular function was performed in a routine manner and recorded every 5 minutes.

All dogs received an IV infusion of a balanced polyionic solution throughout the duration of the anesthetic episode. All dogs in the study also received an IV injection of an antimicrobial (cephazolin) after induction of anesthesia. At the completion of the study and before dogs were allowed to recover from anesthesia, postoperative analgesics were administered. No specific evaluation was made of the surgical outcomes in these dogs.

Vomiting, regurgitation, and GER—Vomiting was defined as gastric contents actively deposited on the floor by a conscious dog. 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 a decrease in esophageal pH to < 4 (reflux of gastric acid) or an increase to ≥ 7.5 (reflux of bile) for a period of ≥ 30 seconds.

Measurement of esophageal pH—Gastroesophageal reflux was determined 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 prior to 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 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 orad 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 anesthetic episode. Analyses of the pH data were performed by use of specific software.

Determination of the study population—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% associated with administration of isoflurane (our control treatment) to 20% for use of other inhalant agents as a clinically meaningful response to treatment. On the basis of a 1-sided type-1 error of 0.05 and power of 0.8, we determined that 30 dogs would be needed in each treatment group to detect this reduction in GER.

It is useful to evaluate the changes in absolute risk of an event associated with a particular treatment to determine the practical importance of a research finding. A good measure of absolute risk is the NNT. When applied to the study reported here, it was the number of anesthetized dogs that a clinician would need to treat with halothane or sevoflurane to cause 1 fewer case of GER. The NNT was calculated by use of the following equation:

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

where \( P_c \) is the incidence of GER in the control group and \( P_e \) is the incidence of GER in the experimental (treatment) group.

Statistical analysis—Summary statistics were computed for each of the risk factors of interest. Normally distributed data were reported as mean ± SD. Statistical analyses were performed on a personal computer by use of commercially available software. The main risk factor of interest was administration of the various inhalants. 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. Age, body weight, dose of thiopental, duration of food withholding, or duration of food withholding (Table 1) at which anesthesia was induced, duration of anesthesia, and duration of surgery were compared among groups by use of a 1-way ANOVA. A \( \chi^2 \) test was used to test categoric variables (vomiting and GER) to detect significant differences among groups.

Results

Animals—Twenty-one breeds of dog were represented in the study, including 30 mixed-breed dogs, 27 Labrador Retrievers, 5 Golden Retrievers, 5 Mastiffs, 4 German Shepherd Dogs, 3 Rottweilers, 2 West Highland White Terriers, and 1 dog each for 14 other breeds. Treatment groups did not differ significantly with regard to body weight, sex distribution, sedation score, dose of thiopental, or duration of food withholding (Table 1). Dogs in the halothane-treated group were significantly younger (1.5 years younger) than dogs in the isoflurane-treated group.

Duration of anesthesia, surgery, and food withholding—Mean ± SD duration of anesthesia was 3.1 ±
0.9 hours, and mean duration of the surgical procedure was 1.8 ± 1.4 hours; these values did not differ significantly among the 3 groups. No morbidity or fatalities were associated with the anesthesia or study protocol. The range for duration of food withholding was 10.5 to 22 hours.

Vomiting, GER, and regurgitation—Forty-three dogs vomited after administration of preanesthetic medications. There was no positive or negative relationship detected between vomiting and subsequent development of GER. Furthermore, there was no relationship detected between duration of food withholding and the incidence of vomiting after administration of preanesthetic medications or incidence of GER during the subsequent anesthetic episode.

Fifty-one of 90 dogs had an episode of GER during anesthesia. The reflux was acidic in all dogs. There were 14, 19, and 18 dogs that had GER during administration of isoflurane, halothane, and sevoflurane, respectively; however, these values did not differ significantly (Table 2). Time of day at which anesthesia was induced was evaluated, and there was no significant (P = 0.3) difference in the time of day that anesthesia was induced between dogs that had GER and those that did not.

Esophageal pH was < 4 for a mean of 64% of the measurement period in the dogs that had GER (Table 2). Total amount of time during which esophageal pH was < 4 and the percentage of the measurement period in which pH was < 4 did not differ significantly among the treatment groups. Dogs that had GER during anesthesia had a median of 1 episode of reflux during the anesthetic period. There was no significant difference in the lowest pH recorded in each of the groups.

Esophageal pH varied little throughout the anesthetic period in the dogs that did not have GER. In those dogs, mean esophageal pH was 6.4 when the probe was initially inserted and 6.0 immediately before the probe was removed.

Sixteen dogs had GER early during the anesthetic episode (ie, in the period between induction of anesthesia and before insertion of the pH sensing probe). This was detected in 6 dogs administered isoflurane, 7 administered halothane, and 3 administered sevoflurane. Perhaps as a result of variability in the data, there was no significant difference among groups in the interval between probe insertion and GER (Table 2).

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, start of surgery, or change in position. In 7 dogs, the onset of GER was within 20 minutes after the start of surgery. In 17 dogs, the onset of GER was within 20 minutes after the administration of the antimicrobial. In 3 dogs, the onset of GER was associated with moving the dog on or off the surgery table. We did not detect a strong relationship between these events and GER.

Thirteen of 90 dogs had GER of such a large volume of fluid that it was seen to drip from the nose or mouth (regurgitation) during anesthesia and surgery. There was no significant difference in the numbers of dogs that regurgitated during administration of the 3 inhalants (Table 2). Dogs that had GER before probe placement (ie, soon after or during induction of anesthesia) were significantly (P = 0.010) more likely to regurgitate during anesthesia. In dogs that had GER before probe placement, there was no difficulty with endotracheal intubation, nor was there evidence of

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Table 1—Signalment, duration of food withholding, sedation score, and thiopental dose in dogs undergoing elective orthopedic surgery during anesthesia maintained by use of 3 inhalant agents.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Isoflurane</th>
<th>Halothane</th>
<th>Sevoflurane</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of dogs</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>ND</td>
</tr>
<tr>
<td>No. of males (No. neutered)</td>
<td>16 (14)</td>
<td>14 (12)</td>
<td>12 (11)</td>
<td>ND</td>
</tr>
<tr>
<td>No. of females (No. spayed)</td>
<td>14 (13)</td>
<td>16 (15)</td>
<td>18 (18)</td>
<td>ND</td>
</tr>
<tr>
<td>Age (y)†</td>
<td>5.1 ± 2.6</td>
<td>3.4 ± 2.4</td>
<td>4.8 ± 2.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Weight (kg)†</td>
<td>34.2 ± 12.7</td>
<td>35.9 ± 10.8</td>
<td>35.6 ± 13.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Duration of food withholding (h)†</td>
<td>16.2 ± 3.1</td>
<td>15.8 ± 2.7</td>
<td>16.8 ± 3.2</td>
<td>0.45</td>
</tr>
<tr>
<td>Sedation (cm)†,‡</td>
<td>3.6 ± 1.9</td>
<td>2.7 ± 2.0</td>
<td>3.1 ± 1.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Thiopental (mg/kg)†</td>
<td>8.4 ± 1.6</td>
<td>9.6 ± 2.5</td>
<td>8.9 ± 2.2</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Means within a row were considered significantly different at P < 0.05. Values reported are mean ± SD. †Sedation was scored by use of a visual analogue scale (scale of 0 to 10 cm; 0 = no evidence of sedation, 10 = heavily sedated). ND = Not determined.

Table 2—Results for dogs undergoing elective orthopedic surgery and evaluated to detect GER during anesthesia maintained by use of 3 inhalant agents.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Isoflurane</th>
<th>Halothane</th>
<th>Sevoflurane</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of dogs</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>ND</td>
</tr>
<tr>
<td>No. that vomited</td>
<td>18</td>
<td>15</td>
<td>11</td>
<td>0.11</td>
</tr>
<tr>
<td>No. with GER</td>
<td>14</td>
<td>19</td>
<td>18</td>
<td>0.39</td>
</tr>
<tr>
<td>No. that regurgitated</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>0.70</td>
</tr>
<tr>
<td>Onset of GER (min)†</td>
<td>42.7 ± 79.2</td>
<td>17.2 ± 31.6</td>
<td>49.9 ± 76.4</td>
<td>0.28</td>
</tr>
<tr>
<td>Duration of GER (min)†</td>
<td>94.7 ± 64.2</td>
<td>100.8 ± 54.5</td>
<td>87.0 ± 57.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Amount of time at pH &lt; 4 (%)†</td>
<td>66 ± 31</td>
<td>66 ± 34</td>
<td>60 ± 30</td>
<td>0.82</td>
</tr>
</tbody>
</table>

See Table 1 for key.
fluid in the pharynx. Mean ± SD interval between probe placement and onset of reflux for all dogs with GER was 35.8 ± 64.7 minutes; this interval did not differ significantly among groups.

NNT—Administration of halothane or sevoflurane was associated with a small increase in absolute risk of developing GER of 16% and 13%, respectively, compared with the risk of developing GER when administered isoflurane. The NNT was 6 for halothane and 8.5 for sevoflurane.

Discussion

The large number of patients at our facility that regurgitate during anesthesia and the steady number of patients that develop severe postanesthetic esophageal dysfunction continue to pique our interest in GER. In the study reported here, 13 of 90 dogs regurgitated; this is higher than the rate reported in other studies (590 dogs,22/270 dogs,2 and 1/240 dogs).6

Onset of GER early during the anesthetic period made a dog more likely to regurgitate during anesthesia. Prolonged exposure of the esophagus to acid probably also places these dogs at greater risk of developing esophagitis. Although we did not survey the owners in this study, none of the dogs had major esophageal problems immediately following anesthesia.

The extremely high incidence of GER during anesthesia in our study group was extremely intriguing. Similar studies6,8 in other populations of dogs reveal rates of GER that are approximately half the rate detected in our population. We have speculated that 1 possible explanation for these differences is the difference between the effect of propionylpromazine and acepromazine. We believe this hypothesis remains the leading contender. An effect of inhalant has also been postulated, which initiated the study reported here.

Acepromazine administered alone prior to anesthesia is associated with an incidence of GER of 29%, with the risk of GER increasing in an apparent dose-dependent manner when morphine is also administered.5 This suggests that acepromazine also has some effect in reducing tone at the gastroesophageal sphincter, which is exacerbated by morphine. Acepromazine also has some antiemetic properties when administered before opioids,7 but it did not prevent morphine-induced emesis in the dogs in our study. Induction of anesthesia with thiopental is associated with a much lower incidence of GER than is the incidence of GER after induction with propofol.6

Induction of anesthesia is associated with a reduction in GESP.6,39 This reduction in GESP is probably associated with an increased risk of GER. In the study reported here, we determined that a 35% reduction in absolute risk of developing GER (63% reduction in relative risk) would be a meaningful response to treatment. In this context, there was no difference in risk of developing GER whether dogs received halothane, sevoflurane, or isoflurane. There would appear to be an increased (17% higher) risk of developing GER during anesthesia maintained by use of sevoflurane than during anesthesia maintained by use of isoflurane. However, a power calculation performed as described previously indicated that we would need 130 dogs in each group to statistically verify this assumption.

Dogs in the group that received halothane were a mean of 1.5 years younger than the dogs in the isoflurane group. This difference was statistically significant but clinically unimportant.

The preponderance of gastric acid reflux in the dogs of the study reported here mirrors the findings for other studies4-6,6 of GER in anesthetized dogs. Increased gastric acidity can cause an increase in the incidence of GER.20,21 Withholding of food for 18 hours can cause a decrease in GESP in awake dogs and may be a factor in the development of GER during anesthesia.3 The impact of our prolonged withholding of food prior to anesthesia on subsequent GER during the anesthetic episode is intriguing and definitely requires additional investigation. It is hoped that an absolute reduction in GER can be achieved as we acquire additional information about the impact of anesthetic agents and other management strategies on the incidence of GER during anesthesia.

Measuring esophageal pH during anesthesia represents a practical assessment of esophageal function of dogs.22 As the number of dogs evaluated for GER during anesthesia increased, the lack of any relationship (positive or negative) between vomiting after administration of preanesthetic medications and subsequent GER has become clear. Emesis is an adverse effect of opioid administration to dogs. It is unpleasant to observe, and clean up of vomitus may be distasteful, but vomiting appears to have no adverse impact on affected dogs.

Calculating the NNT is a way to meaningfully apply the findings from a clinical trial. Basically, this statistic compares the relative risk of a specific event in the study and control population. In the study reported here, the values for NNT were 6 and 8.5. This indicates that there would be 1 additional case of GER for every 6 dogs anesthetized with halothane and every 8.5 dogs anesthetized with sevoflurane, compared with the number of dogs with GER in which anesthesia was maintained with isoflurane.

In the study reported here, we investigated the effects of administration of isoflurane, halothane, or sevoflurane on the incidence of GER in healthy dogs undergoing elective orthopedic surgery. The major finding was that the risk of developing GER was not meaningfully affected by the selection of inhalant for maintenance of anesthesia.

References

2. Wilson DV, Evans AT, Maner WA. Influence of metoclo-


