Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs

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Opioids and nonsteroidal anti-inflammatory drugs (NSAID) have long been used to manage pain in dogs and other animals.1 In animals undergoing general anesthesia with a volatile anesthetic, administration of an opioid decreases the amount of volatile anesthetic that must be administered, as evidenced by a decrease in the minimal alveolar concentration (MAC) of the volatile anesthetic.3 In people, preoperative administration of ketorolac, an NSAID, reduces the requirement for isoflurane during surgery by an amount similar to that observed following administration of opioid analgesics.7 In rats, analgesic potencies of morphine, aspirin, and a morphine-aspirin combination were objectively compared,1 and it was found that the combination of aspirin and morphine resulted in a significantly greater reduction in the amount of isoflurane required for anesthesia than did either drug alone.

Butorphanol is an opioid agonist-antagonist that can be given IV to manage pain in dogs.6 Carprofen is a recently developed NSAID that also has been shown to have analgesic effects in dogs.5 However, whether preoperative administration of butorphanol or carprofen reduces the amount of isoflurane required in dogs undergoing general anesthesia has not, to our knowledge, been determined. Furthermore, whether there is an interaction between butorphanol and carprofen in regard to the decrease in the requirement for isoflurane in dogs has not been evaluated. Therefore, the purpose of the study reported here was to evaluate the effects of butorphanol and carprofen, alone and in combination, on the MAC of isoflurane in dogs.

Materials and Methods

Animals—Six 2- to 3-year-old mixed-breed dogs (3 females and 3 males) with a mean ± SD body weight of 18.0 ± 2.9 kg (39.5 ± 6.3 lb) were used in the study. For all dogs, results of physical examinations, serum biochemical analyses, and CBC performed prior to the study were unremarkable. All dogs had received routine vaccinations and had been dewormed on a regular basis; results of an antibody heartworm test were negative. The study protocol was approved by the Oklahoma State University Animal Care and Use Committee.

Study design and procedure—A randomized complete-block crossover study design was used so that MAC of isoflurane was determined in each dog following administration of carprofen alone, butorphanol alone, carprofen and butorphanol, and neither drug (control). A minimum of 7 days was allowed to elapse between each treatment.

For the first part of the study, food was withheld from all dogs overnight. Dogs were randomly assigned to 1 of 2 groups. Three hours prior to induction of anesthesia, dogs in the first group were given a small amount of canned food without any drugs and dogs in the other group were given an equivalent amount of canned food that did not contain any drugs. Anesthesia was induced by administering isoflurane in

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**Objective**—To evaluate the effects of butorphanol and carprofen, alone and in combination, on the minimal alveolar concentration (MAC) of isoflurane in dogs.

**Design**—Randomized complete-block crossover study.

**Animals**—6 healthy adult dogs.

**Procedure**—Minimal alveolar concentration of isoflurane was determined following administration of carprofen alone, butorphanol alone, carprofen and butorphanol, and neither drug (control). Anesthesia was induced with isoflurane in oxygen, and MAC was determined by use of a tail clamp method. Three hours prior to induction of anesthesia, dogs were fed a small amount of canned food without any drugs (control) or with carprofen (2.2 mg/kg of body weight [1 mg/lb]). Following initial determination of MAC, butorphanol (0.4 mg/kg [0.18 mg/lb], IV) was administered, and MAC was determined again. Heart rate, respiratory rate, indirect arterial blood pressure, end-tidal partial pressure of CO2, and saturation of hemoglobin with oxygen were recorded at the time MAC was determined.

**Results**—Mean ± SD MAC of isoflurane following administration of butorphanol alone (1.03 ± 0.22%) or carprofen and butorphanol (0.90 ± 0.21%) were significantly less than the control MAC (1.28 ± 0.14%), but MAC after administration of carprofen alone (1.20 ± 0.13%) was not significantly different from the control value. The effects of carprofen and butorphanol on the MAC of isoflurane were additive. There were no any significant differences among treatments in regard to cardiorespiratory data.

**Conclusions and Clinical Relevance**—Results suggest that administration of butorphanol alone or in combination with carprofen significantly reduces the MAC of isoflurane in dogs; however, the effects of butorphanol and carprofen are additive, not synergistic. (J Am Vet Med Assoc 2000;217:1025–1028)
A minimum of 7 days later, dogs were anesthetized again, and MAC was determined. However, treatments were reversed so that 3 hours prior to anesthesia, dogs in the first group were given a small amount of canned food that did not contain any drugs, and dogs in the other group were given an equivalent amount of canned food containing carprofen at a dose of 2.2 mg/kg (1 mg/lb).

Statistical analyses—For each of the 3 treatments (carprofen alone, butorphanol alone, and butorphanol and carprofen together), the percentage reduction in the MAC of isoflurane, compared with the control value, was determined by use of the following equation:

\[
\text{percentage reduction} = \text{control MAC} - \text{treatment MAC} \times 100/\text{control MAC}
\]

Values are expressed as mean ± SD. Cardiorespiratory data and MAC were analyzed by use of ANOVA for repeated measures. The least-significant difference test was used for multiple comparisons between treatment means. The experimental design was a 2 × 2 factorial arrangement of treatments in a randomized complete-block design. The 2 factors of interest were butorphanol and carprofen; dogs served as the blocking factor. The interaction of butorphanol and carprofen was used to evaluate whether change in MAC departed from an additive model. If the interaction term was significant, then the effect was synergistic (the combination of butorphanol and carprofen resulted in MAC lower than would have been expected if it was assumed that effects of the 2 drugs were additive) or antagonistic (the combination of butorphanol and carprofen resulted in MAC higher than would have been expected if it was assumed that effects of the 2 drugs were additive). If the interaction term was not significant, then the main effects of butorphanol and carprofen were examined. For all analyses, values of \( P < 0.05 \) were considered significant.

Results

There was no significant (\( P = 0.7 \)) interaction between the effects of butorphanol and carprofen on MAC of isoflurane, indicating that effects of butorphanol and carprofen were simply additive and not synergistic or antagonistic. Administration of butorphanol or of butorphanol and carprofen significantly (\( P < 0.001 \)) decreased the MAC of isoflurane, compared with the control value (Table 1). Although MAC

### Table 1—Effects of carprofen and butorphanol, alone or in combination, on the minimal alveolar concentration (MAC) of isoflurane in dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Carprofen</th>
<th>Butorphanol</th>
<th>Carprofen and butorphanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC (volume %)</td>
<td>1.28 ± 0.14</td>
<td>1.20 ± 0.13</td>
<td>1.03 ± 0.22</td>
<td>0.90 ± 0.21</td>
</tr>
<tr>
<td>Percentage reduction in MAC</td>
<td>NA</td>
<td>6.42 ± 3.24</td>
<td>20.26 ± 12.91</td>
<td>29.46 ± 15.95</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>114.3 ± 27.1</td>
<td>111.5 ± 19.9</td>
<td>94.3 ± 25.4</td>
<td>92.5 ± 20.3</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>105.3 ± 11.6</td>
<td>106.8 ± 7.4</td>
<td>107.3 ± 14.4</td>
<td>114 ± 16.8</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>72.5 ± 6.8</td>
<td>74.2 ± 6.5</td>
<td>73.0 ± 5.7</td>
<td>76.5 ± 11.8</td>
</tr>
<tr>
<td>Saturation of hemoglobin with oxygen</td>
<td>97.6 ± 1.2</td>
<td>96.8 ± 1.0</td>
<td>97.5 ± 0.5</td>
<td>96.7 ± 1.3</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>14.0 ± 7.0</td>
<td>12.8 ± 6.7</td>
<td>12.7 ± 4.4</td>
<td>14.2 ± 7.2</td>
</tr>
<tr>
<td>End-tidal partial pressure of CO2</td>
<td>38.8 ± 2.9</td>
<td>38.3 ± 2.7</td>
<td>38.0 ± 1.0</td>
<td>38.2 ± 3.1</td>
</tr>
</tbody>
</table>

Values represent mean ± SD for 6 dogs.

*Significantly (\( P < 0.05 \)) different from value obtained after administration of carprofen alone.

NA = Not applicable. BP = Blood pressure. Saturation of hemoglobin with oxygen. End-tidal partial pressure of CO2.
was lower after administration of carprofen, compared with the control value. The P value (P = 0.069) was not less than the cutoff for significance. There were not any significant differences among treatments in regard to cardiorespiratory data.

**Discussion**

In the present study, administration of butorphanol alone and butorphanol in combination with carprofen significantly reduced the MAC of isoflurane in dogs; however, the effects of butorphanol and carprofen were additive, not synergistic. Mean ± SD MAC of isoflurane when dogs were not given butorphanol or carprofen (ie, control value) was 1.28 ± 0.14%. This is similar to the MAC of isoflurane reported by Steffey and Howland12 for a larger group of dogs (n = 17).

It has been reported that preoperative administration of carprofen has a greater analgesic effect in the early postoperative period in dogs undergoing ovariohysterectomy than does postoperative administration.1 However, it is not currently known whether preoperative administration of carprofen has an analgesic effect during surgery. In the present study, we tested the hypothesis that preoperative administration of carprofen would reduce the amount of isoflurane, as reflected by the MAC, needed for anesthesia of dogs. We found that preoperative administration of carprofen reduced the MAC of isoflurane by a mean of 6.24 ± 3.42%, compared with the control value. Even though this difference was not significant (P = 0.069), we believe the data provided a strong indication that carprofen may in fact have an effect on the MAC of isoflurane in dogs. There are several reasons why we did not detect a significant reduction in the MAC of isoflurane following administration of carprofen in the present study. Most importantly, carprofen may be a weak analgesic agent; therefore, it has only a weak ability to decrease the amount of isoflurane that must be administered to prevent the dogs from feeling noxious stimuli in this study. Other possible reasons for our inability to detect a significant decrease in MAC are the small sample size used and the limitations of the tail clamp method for determining MAC. The stimulus provided by tail clamping may not adequately mimic the pain and inflammatory responses induced by surgery, and the tail clamp method may, therefore, have failed to detect important beneficial effects of carprofen. This may also help to explain the findings of Alibhai and Clarke,13 who reported that carprofen minimally influenced the MAC of halothane in dogs and used electrical stimulation as the noxious stimulus for determining MAC. Although carprofen only minimally reduced the MAC of isoflurane in the present study, the beneficial effects that preoperative administration of carprofen in dogs has during the early recovery period have been well-demonstrated.15

In contrast to carprofen, butorphanol induced a 20.26 ± 12.91% reduction in MAC of isoflurane in the present study. The reduction in MAC may have been a result of greater analgesia, greater hypnosis, better hyporeflexia, or some combination of these, and our results suggest that butorphanol has a stronger action on these activities than does carprofen. There is conflicting information in the literature regarding the effect of butorphanol on the MAC of inhalant anesthetics in dogs. In 1 study,15 administration of butorphanol at doses up to 0.8 mg/kg (0.36 mg/lb) did not affect the MAC of halothane, whereas in another study,13 administration of butorphanol at a dose of 0.3 mg/kg (0.14 mg/lb) reduced the MAC of enflurane by 15 ± 4%. Differences among the results of previous studies and the present study are likely attributable to differences in the method used to determine MAC and differences in the dose of butorphanol used in each study.

Combinations of analgesic agents have long been used in human patients.1 The most important consideration when formulating analgesic combinations is to combine 2 or more analgesics with different mechanisms of action to enhance analgesia and reduce the risk of adverse effects.2 In the present study, we found the reduction in MAC of isoflurane associated with administration of butorphanol was approximately 3 times and the reduction associated with administration of a combination of butorphanol and carprofen was approximately 5 times the reduction associated with administration of carprofen alone. This was attributed to the additive effects of carprofen and butorphanol on the MAC of isoflurane in dogs.

The potential benefits of decreasing the amount of inhalant anesthetic required for anesthesia include decreases in dose-related cardiorespiratory depressant effects, anesthetic waste gas pollution, and the cost of inhalation anesthesia.14 Isoflurane has dose-dependent depressant effects on respiratory function, blood pressure, and cardiac output in dogs; however, in healthy dogs, the cardiorespiratory effects of isoflurane at the MAC are modest. In the present study, we did not detect any significant differences in cardiopulmonary function among treatments. This failure to observe any beneficial effects on cardiopulmonary function in association with a reduction in isoflurane concentration may have been a result of the small sample size, the lack of sophisticated cardiorespiratory measurement devices, the minimal effect of low doses of isoflurane (1 × MAC) in healthy dogs, or a combination of these factors. Improvements in cardiopulmonary function associated with the isoflurane-sparing effect of the combination of carprofen and butorphanol may be apparent in dogs in a surgical plane of anesthesia (1.2 to 1.5 × MAC)15 and in debilitated patients.

It has been reported that the isoflurane-sparing effects of aspirin and morphine are synergistic in rats,5 and NSAID such as ketorolac have been found to potentiate the antinociceptive effect of morphine in rats.39 Nonsteroidal anti-inflammatory drugs increase the availability of arachidonic acid, which is converted to 12-lipoxygenase, and 12-lipoxygenase presensitizes mu-opioid receptors to the action of mu-opioid agonists.30 In the present study, the effects of carprofen and butorphanol in combination on the MAC of isoflurane were simply additive rather than synergistic. Possible explanations for the lack of a synergistic effect include species variations between dogs and rats and the fact that morphine is a mu-opioid agonist, whereas butorphanol is a kappa-opioid agonist.30
References