Effects of morphine, butorphanol, buprenorphine, and U50488H on the minimum alveolar concentration of isoflurane in cats

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Objective—To determine whether opioids with varying interactions at receptors induce a reduction in minimum alveolar concentration (MAC) of isoflurane in cats.

Animals—12 healthy, female, spayed cats.

Procedure—Cats were anesthetized with isoflurane and instrumented to allow collection of arterial blood and measurement of arterial blood pressure. Each drug was studied separately, and for each drug cats were randomly allocated to receive 2 doses. The drugs studied were morphine (0.1 or 1.0 mg/kg), butorphanol (0.08 or 0.8 mg/kg), buprenorphine (0.005 and 0.05 mg/kg), and U50488H (0.02 and 0.2 mg/kg). All drugs were diluted in 5 ml of saline (0.9% NaCl) solution and infused IV for 5 minutes. The MAC of isoflurane was determined in triplicate, the drug administered, and the MAC of isoflurane redetermined for a period of 3 hours.

Results—All drugs had a significant effect on MAC over time. With morphine only, the effect on MAC over time was different between doses. The greatest mean (±SD) reductions in MAC of isoflurane in response to morphine, butorphanol, buprenorphine, and U50488H administration were 28 ± 9, 19 ± 3, 14 ± 7, and 11 ± 7%, respectively.

Conclusions and Clinical Relevance—Morphine (1.0 mg/kg) and butorphanol (0.08 and 0.8 mg/kg) induced significant reductions in MAC of isoflurane that were considered clinically important. Although significant, reductions in MAC of isoflurane induced by morphine (0.1 mg/kg), buprenorphine (0.005 and 0.05 mg/kg), and U50488H (0.02 and 0.2 mg/kg) were not clinically relevant because they fell within the error of the measurement technique. Administration of morphine or butorphanol decreases the need for potent inhalant anesthetics in cats and could potentially be beneficial in combination with inhalants.

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rane in oxygen (2 L/min), delivered via a circle breathing sys-
tem. Once anesthesia was induced, the trachea was intubated, and anesthesia was maintained with isoflu-
range was delivered. Once anesthesia was induced, the trachea
ratchet caught.

Applying a 10-in hemostat to the base of the tail until the
anesthetic concentration. The MAC was then tested by
analysing any response. If no response occurred, the end-
tidal anesthetic concentration was increased by 10%; if any
response occurred, the end-tidal anesthetic concentration
was decreased by 20% rather than 10%, held stable for
at least 20 minutes, and MAC was retested. The MAC
was then determined by use of the method described, and
to quantify the effect of opioid administration, MAC determi-
nation was continued for a period of 3 hours following drug
administration. Prior to each MAC determination, arterial
blood pressure and heart rate were measured, and blood
was obtained for measurement of gas tensions and pH.

### Experimental protocol

After instrumentation, the cat was maintained for at least 20 minutes at a stable end-tidal
anesthetic concentration. The MAC was then tested by
applying a 10-in hemostat to the base of the tail until the
ratch was caught. The tail was moved continuously with the
hemostat for 1 minute while observing the cat for gross pur-
poseful movement. If no response occurred, the end-tidal
anesthetic concentration was decreased by approximately
10%; if any response occurred, the end-tidal
anesthetic concentration was decreased by 20% rather than 10%, held stable
at least 20 minutes, and MAC was retested. The MAC
was then determined by use of the method described, and
to quantify the effect of opioid administration, MAC determi-
nation was continued for a period of 3 hours following drug
administration. Prior to each MAC determination, arterial
blood pressure and heart rate were measured, and blood
was obtained for measurement of gas tensions and pH.

### Table 1—Mean (± SD) isoflurane minimum alveolar concentration (MAC) after IV administration of morphine, butorphanol, buprenor-
phine, and USO488H in 6 cats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Baseline</th>
<th>0 min</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>P values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.1</td>
<td>1.60 ± 0.10</td>
<td>1.42 ± 0.16</td>
<td>1.41 ± 0.15</td>
<td>1.43 ± 0.23</td>
<td>1.44 ± 0.23</td>
<td>0.2499</td>
</tr>
<tr>
<td>1.0</td>
<td>1.58 ± 0.07</td>
<td>1.20 ± 0.24</td>
<td>1.19 ± 0.23</td>
<td>1.22 ± 0.20</td>
<td>1.17 ± 0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.08</td>
<td>1.54 ± 0.12</td>
<td>1.26 ± 0.08</td>
<td>1.26 ± 0.06</td>
<td>1.42 ± 0.15</td>
<td>1.41 ± 0.15</td>
<td>0.2476</td>
</tr>
<tr>
<td>0.8</td>
<td>1.54 ± 0.19</td>
<td>1.24 ± 0.17</td>
<td>1.27 ± 0.18</td>
<td>1.31 ± 0.16</td>
<td>1.30 ± 0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.005</td>
<td>1.20 ± 0.13</td>
<td>1.06 ± 0.13</td>
<td>1.09 ± 0.17</td>
<td>1.10 ± 0.20</td>
<td>1.11 ± 0.14</td>
<td>0.5678</td>
</tr>
<tr>
<td>0.05</td>
<td>1.27 ± 0.13</td>
<td>1.09 ± 0.11</td>
<td>1.10 ± 0.11</td>
<td>1.14 ± 0.11</td>
<td>1.13 ± 0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USO488H</td>
<td>0.02</td>
<td>1.24 ± 0.17</td>
<td>1.21 ± 0.27</td>
<td>1.28 ± 0.23</td>
<td>1.17 ± 0.14</td>
<td>1.22 ± 0.13</td>
<td>0.1586</td>
</tr>
<tr>
<td>0.2</td>
<td>1.25 ± 0.18</td>
<td>1.13 ± 0.15</td>
<td>1.12 ± 0.17</td>
<td>1.15 ± 0.19</td>
<td>1.14 ± 0.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 considered significant.
Buprenorphine is a partial μ-agonist and, as such, its efficacy is limited when compared with full agonists. As a result, the initial part of the dose-response curve is similar to that of full agonists, but the maximal analgesia produced is less. Butorphanol is a κ-agonist, with slight μ-antagonistic properties. Agonist-antagonists have a lower maximal efficacy, compared with full agonists; however, as a κ-agonist, butorphanol is associated with less excitement in cats.11 For each drug, 2 doses were selected in which a 10-fold difference was observed between the low and the high dose. The low dose was usually at or just below the clinical dose range, and the high dose was usually above the clinical dose range. It was hoped that this magnitude of difference in dose would enable, if appropriate, significant dose effects to be determined. Because of the rapidly changing plasma concentration following a single IV bolus of drug and the time-consuming method of determining MAC, we were unable to precisely define the peak magnitude or the maximal isoflurane sparing effect for the drugs from our study. It was envisaged that results from our study could be used to select drugs with appropriate receptor interactions for further study by use of increasing steady-state concentrations.

In our study, the isoflurane control MAC values were different between cat populations, although they were consistent within each cat population. In the first group, the control MAC values were 1.60, 1.58, 1.54, and 1.54% for the 4 studies, whereas in the second group, the values were 1.20, 1.27, 1.24, and 1.25%. In the second group, the values were similar to published values of 1.63 ± 0.0216 and 1.61 ± 0.04%.16 In the second group, the values are similar to published values of 1.16 and 1.28 ± 0.13%.16 It is difficult to explain these differences in reported MAC values in various studies, because MAC values between animals of the same species are reported to vary by only 10 to 20%.17 The difference in our study could possibly be attributable to age differences of cats between experiments. In the first group, the age was 1.75 ± 0.30 years, whereas in the second group, the age was 4.92 ± 2.18 years. Although age-related changes in MAC of inhalant anesthetics have not been investigated in animals, in humans the MAC of halothane has been reported to decrease with increasing age.18

Table 2—Mean (± SD) reduction in MAC of isoflurane after IV administration of morphine, butorphanol, buprenorphine, and USO488H in 6 cats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>0 min</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.1</td>
<td>11 ± 4</td>
<td>12 ± 4</td>
<td>11 ± 10</td>
<td>11 ± 10</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>25 ± 12</td>
<td>25 ± 12</td>
<td>23 ± 10</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.08</td>
<td>18 ± 4</td>
<td>18 ± 4</td>
<td>8 ± 7</td>
<td>9 ± 7</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>19 ± 3</td>
<td>18 ± 4</td>
<td>15 ± 5</td>
<td>15 ± 10</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.005</td>
<td>11 ± 6</td>
<td>9 ± 5</td>
<td>9 ± 10</td>
<td>8 ± 7</td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>14 ± 7</td>
<td>13 ± 7</td>
<td>10 ± 11</td>
<td>10 ± 11</td>
</tr>
<tr>
<td>USO488H</td>
<td>0.02</td>
<td>2 ± 9</td>
<td>3 ± 5</td>
<td>4 ± 4</td>
<td>0 ± 9</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>9 ± 4</td>
<td>10 ± 4</td>
<td>8 ± 4</td>
<td>11 ± 7</td>
</tr>
</tbody>
</table>

Significant differences in systolic, diastolic, and MAP, as well as heart rate, were found between the 2 morphine doses. For both doses, body temperature, PaCO₂, and arterial pH had significant changes over time. The effect on body temperature, PaCO₂, arterial pH, and BD over time was different between the 2 doses.

Following butorphanol administration, a significant effect of dose was not found; however, PaCO₂, arterial pH, arterial HCO₃ concentration, and BD had significant changes over time. For all other values, no time effects or interactions between time and dose were found.

Following buprenorphine administration, no significant effect of dose was found; however, PaCO₂ and BD had significant changes over time. For all other values, no time effects or interactions between time and dose were found.

Following USO488H administration, no significant effects of dose or time were found; however, the effect on body temperature and arterial pH over time was different between the 2 doses. For all other values, no interactions between time and dose were found.

**Discussion**

In our experiments, each drug was studied independently, and the experiments were not designed to compare results between experiments. The reasons for this were twofold; firstly, because of the difficulty with instrumentation in cats, we needed to have 2 separate populations and secondly, because of a paucity of information on cats, there is difficulty in determining equipotent doses. To control physiologic variables that could induce changes in MAC of isoflurane, the femoral artery was catheterized to measure direct arterial blood pressure and to collect arterial blood for measurement of blood gas and pH values. Although the arteries were sutured rather than ligated, it is sometimes difficult to catheterize the same artery more than twice.

Our drug selection included 4 opioids each with varying interactions at the opioid receptors. Morphine, as a full μ-agonist opioid, induces profound analgesia; however, excitement and mania (at high doses) is common in cats.11 USO488H is a selective κ-agonist opioid. The advantage of drugs with agonist activity at the κ-receptor, compared with the μ-receptor, is that they induce profound analgesia with less likelihood of excitement in species such as horses and cats.13
investigated opioid-induced reductions in MAC of inhalant anesthetics.

Although no statistical comparisons were made in our study between drug effects, the reduction in MAC of isoflurane for morphine is greater than that for the other drugs. The greatest reduction in MAC of isoflurane for butorphanol, buprenorphine, and U50488H were 19 ± 3, 14 ± 7, and 11 ± 7%, respectively. Because of the bracketing method used in determining MAC, changes of approximately 10% are not considered clinically important, because they fall within the error of the measurement technique. When the mean and SD are considered, low dose morphine and both doses of buprenorphine and U50488H fall within the 10% measurement error.

Reduction in MAC of inhalant anesthetics has been reported to be species and opioid dependent. A number of opioids have been studied in dogs, and those with agonist properties at the μ-receptor are reported to induce greater maximal reduction in MAC of inhalants than those that exert effects at other receptors. Morphine, fentanyl, alfentanil, and sufentanil are full μ-agonist drugs, and their reported maximal reduction in MAC of inhalants in dogs are 63 ± 3%, 64.4 ± 4%, 68.5 ± 6%, and 56.5 ± 7.3%, respectively. In contrast, the effects on MAC after butorphanol administration in dogs are variable and range from 11 ± 2 (at 0.1 mg/kg) to 20 ± 13 (at 0.4 mg/kg, IV) or have no effect (at 0.2, 0.4, and 0.8 mg/kg, IV). Reduction in MAC of inhalants induced by buprenorphine or U50488H administration has not, to our knowledge, been reported for dogs. However, in rats, U50488H administration induced maximal reductions in MAC of halothane of 63 ± 5.5%, and in humans, buprenorphine induced reductions in MAC of halothane of 34%. Although our reduction in MAC of isoflurane for butorphanol of 19 ± 3% in cats is similar to that reported for dogs after administration of butorphanol at a dosage of 0.4 mg/kg, our results of reductions in MAC of isoflurane for buprenorphine and U50488H are less than those reported for humans and rats. In our study, results of neither experiment revealed maximal reduction in MAC following buprenorphine administration, so comparison is questionable; however, full μ-agonists do not induce the same degree of reduction in MAC of inhalants in cats as in humans, so it could be expected that the degree of reduction in MAC of isoflurane induced by partial agonists would also be less. In contrast, U50488H in rats appeared to induce a similar reduction in MAC of inhalants as full μ-agonists, whereas the reduction in MAC of isoflurane in our study was negligible. The reason for the lack of reduction in MAC of isoflurane in our study may be dose related. Our doses were extrapolated from work in horses where 0.2 mg/kg induced pronounced ataxia, and an upper limit of 0.16 mg/kg was recommended. In rats, the shape of the reduction in MAC of halothane versus the dose curve suggested a narrow dose range. In that study, the doses administered were 3, 10, and 30 mg/kg, with each dose inducing 0 ± 0, 41.7 ± 8.6, and 63.0 ± 5.5% reduction in MAC of halothane, respectively. The authors commented that the reductions in MAC of halothane by U50488H at 30 mg/kg were comparable to the effects of morphine at 10 mg/kg and that this ratio in potency was similar to other assays of analgesia. If this were the case in cats, then our selected doses would not have been high enough to induce a reduction in MAC of isoflurane.

Species differences in reductions in MAC of isoflurane induced by opioids have been reported previously, in which IV administration of 2 mg of morphine/kg induced 53% reduction in MAC of isoflurane in monkeys, 50% in dogs, and 13% in swine. That study did not determine maximal reduction in MAC of isoflurane for morphine but rather the greatest effect in each species after a similar dose. The reduction of MAC of 50% for dogs in that study is similar, although lower, than the maximal reduction in MAC of enflurane of 63 ± 3% reported previously for dogs. The reason for species differences is unknown.

In our study, significant dose effects on cardiovascular variables were found for morphine only. On closer examination, variables at all time points, including baseline, were higher for 1.0 mg/kg than 0.1 mg/kg. In cats, morphine has been reported to cause a biphasic response on blood pressure with low doses, inducing a transient increase followed by a decrease and high doses inducing a sustained increase. However, in our study, because of the difference at all time points including the baseline, no conclusions can be drawn.

In our study, significant time effects were found for morphine, butorphanol, and buprenorphine. The measurements affected were usually body temperature, PaCO2, arterial pH, and BD. Closer inspection of the mean (± SD) values for these measurements did not indicate any pattern, and the changes reported are small and not considered to be of clinical importance. These changes are likely not related to the drugs but to subtle changes in exterior warming of the patient and in ventilation delivered by the respirator.

References