The Enflurane Sparing Effect of Sufentanil in Dogs

Richard I. Hall, M.D., F.R.C.P.(C.),* Michael R. Murphy, M.D.,† Carl C. Hug, Jr., M.D., Ph.D.‡

There is a ceiling to the reduction of enflurane MAC by fentanyl in the dog. Sufentanil (SUF), a more potent narcotic, may be more efficacious in reducing enflurane MAC. To test this hypothesis, 25 mongrel dogs were studied in three groups. Group 1 (n = 8) received SUF in progressively increasing infusion rates from 0.005 μg·kg⁻¹·min⁻¹ to a maximum of 1.215 μg·kg⁻¹·min⁻¹. MAC was determined at stable SUF concentrations in plasma [SUF] during each infusion rate. Group 2 (n = 10) received SUF at a dose rate (0.007 μg·kg⁻¹·min⁻¹) designed to produce approximately 35% MAC reduction, and MAC determinations were made at regular intervals over a mean infusion time of 7.6 ± 0.49 h (mean ± SEM). Group 3 (n = 7) received 1.215 μg·kg⁻¹·min⁻¹ and were studied as in group 2 over an infusion time of 6.7 ± 0.42 h. In group 1, the highest infusion rate (1.215 μg·kg⁻¹·min⁻¹) produced [SUF] = 48 ng/ml and reduced MAC by 71 ± 6%. This was not statistically different from the reduction which occurred at [SUF] = 0.92 ng/ml (57 ± 7%; infusion rate 0.015 μg·kg⁻¹·min⁻¹; P = 0.21). In group 2, the degree of MAC reduction achieved by stable [SUF] (0.54 ± 0.08 ng/ml) declined over time (MAC reduction at start = 34 ± 2% versus 18 ± 4.9% at the end of the infusion; P = 0.001), suggesting the development of tolerance. In group 3 (1.215 μg·kg⁻¹·min⁻¹), there was no statistically significant difference demonstrated between the degree of MAC reduction at the beginning versus the end of the infusion. The maximum reduction achieved by an infusion of 1.215 μg·kg⁻¹·min⁻¹ (group 3) for nearly 7 h did not differ from that achieved with a series of progressively increasing infusion rates up to 1.215 μg·kg⁻¹·min⁻¹ (group 1) to 70.5% reduction at [SUF] = 48 versus group 3—78% at 41 ng/ml). The authors conclude that there was a ceiling of approximately 70% reduction of enflurane MAC by SUF in the dog. This reduction was independent of the dose-rate at which it was achieved. At plasma concentrations below those producing a maximum reduction of MAC, acute tolerance was evident. (Key words: Anesthetics, intravenous; infusions; narcotic; sufentanil. Anesthesiology, volatile: enflurane. Potency, anesthetic: ED₉₀; enflurane; MAC; sufentanil; tolerance.)

CENTRAL NERVOUS SYSTEM depressants reduce the minimum alveolar concentration (MAC) of volatile anesthetics.¹⁻⁰ Conceivably, the degree of MAC reduction is a measure of a drug’s ability to act as an anesthetic. The narcotic analgesics, fentanyl and sufentanil, are currently being used as anesthetics, but there have been reports of patient awareness.¹⁰ Attempts to prevent awareness have led to the use of extremely high doses of these agents. Murphy and Hug demonstrated a ceiling effect for fentanyl in terms of its ability to reduce enflurane MAC in the dog.⁶ Sufentanil, a more potent narcotic, may be more efficacious as an anesthetic and capable of reducing enflurane MAC to a greater extent.⁸ This study was performed to determine: 1) to what degree sufentanil can reduce enflurane MAC in the dog; 2) if the sequence of dosing (i.e., progressively increasing infusion rates versus the highest dose-rate to start) makes any difference in the degree of MAC reduction; and 3) the stability of MAC reduction by sufentanil over time.

Materials and Methods

This protocol was approved by the Emory University Animal Use and Care Committee, and followed guidelines established by the National Institutes of Health for the ethical use of animals in research.

Hydrated fasting mongrel dogs (n = 25) weighing 17.6 ± 0.6 kg (all values expressed as the mean ± SEM) were each given an intravenous injection of succinylcholine (0.1 mg/kg) and atropine (0.1 mg/kg), and anesthesia was immediately induced with 5% enflurane in oxygen, administered via a specially designed mask and a Bain anesthesia circuit. Auffed endotracheal tube was introduced, and the dog was ventilated with a Harvard respirator to maintain a normal PaCO₂ and pH. An intravenous catheter was placed in a foreleg vein and 5% dextrose in lactated Ringers solution was administered at a rate of 9.2 ± 0.4 ml·kg⁻¹·hr⁻¹. A urinary bladder catheter was inserted. Temperature was monitored using an esophageal temperature probe and maintained over the course of the anesthetic (9.5 ± 0.3 °C) within 1.9° C of the temperature recorded at the beginning by the use of a warming blanket. The electrocardiogram was monitored throughout the experimental period. A femoral arterial cannula was utilized for continuous blood pressure recording and for periodic sampling of blood for gas analysis and for the determination of sufentanil concentration in plasma. End-tidal enflurane concentration was measured by a Beckman LB-2® infrared analyzer.

MAC determinations were made according to the technique of Eger et al.¹¹ Briefly, the base of the tail was shaved. At least 1 h after the induction of anesthesia and with a stable end-tidal enflurane concentration maintained for at least 15 min, a ‘spoon stick’ clamp was applied to the base of the tail and closed to fill ratchet lock. The tail was moved continuously for 1 min.

Received from the Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia. Accepted for publication May 18, 1987. Supported in part by a grant from Janssen Pharmaceuticals. Presented in part at the 1986 Annual Meeting of the American Society of Anesthesiologists in Las Vegas, Nevada.

Address reprint requests to Dr. Hug; Section of Anesthesiology, The Emory Clinic, 1365 Clifton Road, N.E., Atlanta, Georgia 30322.

* Merck, Sharp, and Dohme International Fellow in Clinical Pharmacology, Associate in Anesthesiology.
† Associate Professor of Anesthesiology.
‡ Professor of Anesthesiology and Pharmacology.

518
or until purposeful movement was elicited from the dog. Following determination of the response to the tail-clamp stimulus, the end-tidal enflurane concentration was adjusted by 0.2% either up or down as appropriate, and the response to stimulation was again determined. Purposeful movement was defined as gross movement of the head or extremities, and did not include coughing, chewing, swallowing, or an increased respiratory effort. MAC was determined to be that concentration (to the nearest 0.1%) midway between the stable end-tidal concentrations of enflurane (maintained for at least 15 min) at which the animal did or did not move in response to the applied stimulus.

Following determination of the control enflurane MAC, the animals were divided into three groups. Group 1 (n = 8) received sufentanil (all doses expressed as the base) in a series of increasing infusion rates. The approach to stable sufentanil concentrations in plasma was hastened by giving a priming infusion over 20 min and simultaneously starting the maintenance infusion at a constant rate. At the end of a 1-h infusion period during which plasma concentrations of sufentanil stabilized, MAC determinations were repeated in the manner previously described. Each animal received at least three different infusion rates (table 1). Arterial blood samples for sufentanil analysis were obtained 45 min from the start of each new infusion rate and then every 15 min until the determination of MAC was completed for each of the infusion rates. Equal volumes of purified protein derivative or 5% albumin were used to reise blood volume lost through sampling. Group 2 (n = 10) received sufentanil 1.5 μg/kg over 20 min and simultaneously, a maintenance infusion of 0.005 μg·kg⁻¹·min⁻¹ was started. MAC was determined 1 h later as described. It was anticipated that this would provide approximately 35% enflurane MAC reduction based on the results obtained from group 1. If at least 30% MAC reduction did not occur (n = 2), the maintenance infusion rate was increased to 0.015 μg·kg⁻¹·min⁻¹, and a further 1-h period of observation was allowed to elapse prior to any further MAC determinations. The mean infusion rate for group 2 was 0.007 μg·kg⁻¹·min⁻¹. The maintenance infusion rate was constant throughout the experiment, and MAC was determined at regular intervals at least 1 h apart (mean duration of infusion 7.6 ± 0.43 h). Group 3 (n = 7) was studied in exactly the same way as group 2, except that the priming dose (365 μg/kg infused over 20 min) and the maintenance infusion rate (1.215 μg·kg⁻¹·min⁻¹) were higher and the time to complete at least three successive MAC determinations at regular intervals was slightly shorter (6.7 ± 0.42 h).

For groups 2 and 3, blood samples for analysis of sufentanil in plasma were collected beginning 45 min

<table>
<thead>
<tr>
<th>Dog</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.5/0.005</td>
<td>1.5/0.01</td>
<td>3/0.02</td>
<td>27/0.135</td>
</tr>
<tr>
<td>11</td>
<td>1.5/0.005</td>
<td>3.0/0.015</td>
<td>9/0.045</td>
<td>108/0.405</td>
</tr>
<tr>
<td>12</td>
<td>1.5/0.005</td>
<td>3.0/0.015</td>
<td>9/0.045</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1.5/0.005</td>
<td>3.0/0.015</td>
<td>9/0.045</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1.5/0.005</td>
<td>3.0/0.015</td>
<td>9/0.045</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1.5/0.005</td>
<td>120/0.405</td>
<td>243/1.215</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.5/0.005</td>
<td>120/0.405</td>
<td>243/1.215</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1.5/0.005</td>
<td>120/0.405</td>
<td>243/1.215</td>
<td></td>
</tr>
</tbody>
</table>

* Priming dose/maintenance infusion rate. The priming dose (μg/kg) was infused at a constant rate over 20 min. The maintenance infusion rate (μg·kg⁻¹·min⁻¹) was constant from the beginning to the end of each dose period and was in addition to the priming dose.

Table 1. Schedule of Infusions*—Group 1

The sufentanil concentration in plasma was determined by radioimmunoassay,§ which incorporated the suggestions made by Schuttler and White.12,13 Our method differed from that of Schuttler and White in the use of BSA-buffer throughout the assay in place of blank plasma. In addition, for sample aliquots greater than 100 μl, correction for possible additional non-specific binding in the plasma was made by analyzing the equivalent volume of control plasma made up to volume with the BSA-buffer. Counts (liquid scintillation spectrometry) due to non-specific binding were subtracted from the unknown sample counts prior to estimation of sufentanil concentration from the concentration versus cpm regression line. The within-assay variation was 4.4%. Between assay variation was 7.6% for concentrations below 1 ng/ml, 3.2% for concentrations from 1–10 ng/ml, and 2.2% for concentrations above 1 ng/ml.

Linear regression analysis was performed to determine the slope of the line representing the plasma concentration versus infusion rate. The mean percentage reduction of enflurane MAC produced by any infusion rate was compared to that produced by other infusion rates by one-way analysis of variance. For groups 2 and 3, the mean percentage reduction in MAC was determined after the first 45 min of the infusion (MAC 2; tables 2, 3) and compared by t test with the final degree of MAC reduction observed at MAC 4 (the last MAC determination in which all animals of both groups were

Table 2. Summary of Results for Group 2

<table>
<thead>
<tr>
<th>Sequence of MAC Determinations</th>
<th>MAC 1 (Control)</th>
<th>MAC 2</th>
<th>MAC 3</th>
<th>MAC 4</th>
<th>MAC 5</th>
<th>MAC 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of dogs</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Enflurane MAC</td>
<td>2.19 ± 0.09</td>
<td>1.44 ± 0.07†</td>
<td>1.61 ± 0.10†</td>
<td>1.68 ± 0.19†</td>
<td>1.86 ± 0.06 †‡</td>
<td>1.87 ± 0.05 †‡</td>
</tr>
<tr>
<td>Percent reduction of MAC</td>
<td>0</td>
<td>34.5 ± 1.8†</td>
<td>26.6 ± 3.7†</td>
<td>22.5 ± 4.9 †‡</td>
<td>13.8 ± 3.7 †‡</td>
<td>12.5 ± 4.0 †‡</td>
</tr>
<tr>
<td>Sufentanil ng/ml of plasma</td>
<td>0</td>
<td>0.52 ± 0.07</td>
<td>0.56 ± 0.10</td>
<td>0.54 ± 0.08</td>
<td>0.47 ± 0.05</td>
<td>0.49 ± 0.05</td>
</tr>
<tr>
<td>Cumulative infusion time (min)</td>
<td>0</td>
<td>154 ± 21</td>
<td>266 ± 19</td>
<td>356 ± 17</td>
<td>444 ± 25</td>
<td>506 ± 28</td>
</tr>
<tr>
<td>Cumulative dose of sufenanil (μg/kg)</td>
<td>0</td>
<td>3.09 ± 0.62</td>
<td>3.60 ± 0.72</td>
<td>4.49 ± 0.76</td>
<td>5.47 ± 1.19</td>
<td>6.66 ± 1.64</td>
</tr>
</tbody>
</table>

* Values represent mean ± SEM
† P < 0.05 vs Control
‡ P < 0.05 vs MAC 2

Results

Group 1

The sufentanil concentration maintained in plasma during MAC determinations was proportional (r = 0.9996, P = 0.001) to the maintenance infusion rate (table 4; fig. 1). The lowest mean concentration in these studies, 0.51 ± 0.08 ng/ml, reduced enflurane MAC by 49.2 ± 5.1%. Higher concentrations produced greater reductions but a ceiling effect was apparent (fig. 2). The maximum reduction of 70.5 ± 5.7% at a plasma sufentanil concentration of 48 ± 8 ng/ml was not statistically greater than the 56.5 ± 7.3% reduction evident at 0.92 ± 0.19 ng/ml (P = 0.51, F = 0.81).

Group 2

When the sufentanil infusion was maintained at a constant low rate (average rate = 0.007 μg·kg⁻¹·min⁻¹ for over 7 h) the plasma concentration of sufentanil remained stable (table 2). The mean of the slopes of the sufentanil plasma concentration versus time regression lines (−0.0002 ng·ml⁻¹·min⁻¹) was not different from zero (n = 10, P = 0.22). The reduction of enflurane MAC at this low constant infusion rate of sufentanil decreased progressively over time when the MAC reduction observed at the beginning of the infusion was compared to that obtained at the end (P = 0.003). This decrease was observed in five out of ten animals, with the remaining five demonstrating either no change (n = 4) or a slight increase (n = 1) in the degree of MAC reduction (fig. 3). The mean of the slopes of the MAC reduction vs time regression lines (−0.056% reduction of enflurane MAC per minute) demonstrated a significant difference from zero (n = 10, P = 0.007).

Group 3

At the higher constant infusion rate (1.215 μg·kg⁻¹·min⁻¹), there was a decrease in the reduction of enflurane MAC over time (table 3), but this failed to

Table 3. Summary of Results for Group 3

<table>
<thead>
<tr>
<th>Sequence of MAC Determinations</th>
<th>MAC 1 (Control)</th>
<th>MAC 2</th>
<th>MAC 3</th>
<th>MAC 4</th>
<th>MAC 5</th>
<th>MAC 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of dogs</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Enflurane MAC</td>
<td>2.41 ± 0.15</td>
<td>0.54 ± 0.08†</td>
<td>0.51 ± 0.07†</td>
<td>0.61 ± 0.11†</td>
<td>0.70 ± 0.17†</td>
<td>0.79 ± 0.29†</td>
</tr>
<tr>
<td>Percent reduction of MAC</td>
<td>0</td>
<td>78.0 ± 2.3†</td>
<td>79.0 ± 2.4†</td>
<td>73.6 ± 4.2†</td>
<td>71.3 ± 6.1†</td>
<td>65.2 ± 11.0†</td>
</tr>
<tr>
<td>Sufentanil ng/ml of plasma</td>
<td>0</td>
<td>51 ± 4.7</td>
<td>45 ± 2.2</td>
<td>39 ± 2.5</td>
<td>35 ± 2.7</td>
<td>33 ± 3.8</td>
</tr>
<tr>
<td>Cumulative infusion time (min)</td>
<td>0</td>
<td>111 ± 7</td>
<td>206 ± 9</td>
<td>294 ± 14</td>
<td>385 ± 14</td>
<td>450 ± 7</td>
</tr>
<tr>
<td>Cumulative dose of sufenanil (μg/kg)</td>
<td>0</td>
<td>501 ± 8</td>
<td>608 ± 10</td>
<td>725 ± 11</td>
<td>829 ± 11</td>
<td>918 ± 12</td>
</tr>
</tbody>
</table>

* Values represent mean ± SEM.
† P < 0.05 vs control.
reach statistical significance \((P = 0.17)\). Examination of the mean of the slopes of the MAC reduction versus time regression lines \((-0.032\% \text{ reduction of enflurene MAC per minute})\) demonstrated no significant difference from zero \((n = 7, P = 0.11)\). In this group, three animals showed a decrease in enflurene MAC over time, two demonstrated no change, and two had a slight increase over time (fig. 3). Comparison of the mean of the slopes of the concentration versus time regression lines \((-0.046 \text{ ng} \cdot \text{ml}^{-1} \cdot \text{min}^{-1})\) showed a significant difference from zero \((n = 7, P = 0.042)\).

The reduction of enflurene MAC was similar when the sufentanil concentration in plasma was achieved early with the initial infusion rate (group 3, table 3, MAC2) and when the equivalent sufentanil concentration was reached late in the experiment after a series of incremental infusion rates (group 1, table 4): 78% MAC reduction at 51 ng/ml in group 3 versus 71% MAC reduction at 48 ng/ml in group 1.

The heart rate and blood pressure data for all animals are shown in table 5. There was an initial fall in heart rate with the initiation of the first sufentanil infusion \((P = 0.0001)\). A further decline \((P = 0.01)\) was observed following institution of the 0.015 \mu g \cdot kg^{-1} \cdot min^{-1} infusion rate, and the maximum decrease in heart rate followed initiation of the 0.405 \mu g \cdot kg^{-1} \cdot min^{-1} infusion rate. Blood pressure declined from the control level (enflurene alone) with the initiation of sufentanil at an infusion rate of 0.015 \mu g \cdot kg^{-1} \cdot min^{-1}; P < 0.05). The maximum decline occurred with the next infusion rate (0.045 \mu g \cdot kg^{-1} \cdot min^{-1}; P < 0.05). Recovery to the control level (0.405 \mu g \cdot kg^{-1} \cdot min^{-1}; P > 0.05) or above (1.215 \mu g \cdot kg^{-1} \cdot min^{-1}; P < 0.05) was evident at the two highest infusion rates (table 5). No animal required hemodynamic therapy or resuscitation. Application of the tail-clamp stimulus produced a consistent rise in heart rate and blood pressure. When the hemodynamic responses after application of the tail-clamp which produced movement in the dogs are compared to the responses when no movement occurred, no significant differences were observed, although the degree of change in hemodynamic responses tended to be greater when a movement response was elicited.

**Discussion**

Sufentanil is a potent narcotic analgesic currently being employed as an anesthetic.14,15 Murphy and Hug have previously reported a ceiling effect for fentanyl in terms of its ability to reduce enflurene MAC (66% at a plasma concentration of 30 ng/ml).6 Hecker et al. were able to demonstrate a 90% reduction in halothane MAC in rats given sufentanil suggesting that this new narcotic might be more efficacious as an anesthetic.8 In their study, a plateau effect occurred at 0.11 \mu g \cdot kg^{-1}, min^{-1}. Plasma sufentanil levels were not measured. While 90% MAC reduction was achieved in terms of tail-clamp response, the rats could still open their eyes and lift their heads to other forms of stimulation. In the present study, the maximum reduction of enflurene MAC in dogs \((70.5 \pm 5.6\%)\) was achieved at an infusion rate of 1.215 \mu g \cdot kg^{-1} \cdot min^{-1} (group 1; table 4). This
maintained an average plasma concentration of 48 ng/ml. At end-tidal concentrations of enflurane which produced no movement, no other somatic responses to other stimuli (e.g., loud noise) were elicited. The absence of plasma concentration data in the study of Hecker et al.\textsuperscript{8} makes further comparison of the two studies difficult.

It has been suggested that the ceiling effect reported in previous studies with fentanyl reflected the use of inadequate doses.\textsuperscript{15} An attempt has been made to address this criticism in the present study. Sufentanil is 5–10 times more potent than fentanyl.\textsuperscript{14,16} The maximum sufentanil dose used in this study is equivalent to a fentanyl dose of 2.2–4.4 mg/kg in the first hour following which the enflurane MAC reduction averaged 78% (group 3; table 3). For each additional hour of sufentanil infusion, the fentanyl-equivalent dose increased by 0.36–0.73 mg/kg, and the total fentanyl-equivalent dose averaged 4.1–8.3 mg/kg over a 6-h period, at which time the reduction of enflurane MAC averaged 65%. It seems unlikely that inadequate doses can be the explanation for the ceiling effect consistently observed in dogs.

Narcotic analgesics produce their effects by binding to specific opioid receptors, of which there are a finite number in the CNS.\textsuperscript{17–19} It is logical to assume that the maximum possible effect of a narcotic would be produced when all opioid receptors were occupied and, accordingly, a ceiling to the intensity of its effect would be expected. This ceiling has been evident in attempts to reduce enflurane MAC in the dog. However, there are two issues to be considered. First, given the high degree of lipophilicity of fentanyl and sufentanil, it is conceivable that they could act like true anesthetics at very high concentrations. Indeed, Dodson and Miller, utilizing a leucine-enkephalin opioid, have provided evidence of both opioid receptor-dependent and non-specific mechanisms (related to lipid solubility and reversible by pressure) in the loss of righting reflex in tadpoles (amphibian).\textsuperscript{20} Sufentanil concentrations above 50 ng/ml (0.13 micromolar) may be required to exert a non-specific anesthetic action, since typical anesthetics are effective in micromolar concentrations. In humans, Philbin et al.\textsuperscript{21} were unable to suppress either catecholamine release or hemodynamic responses to surgical stimulation in patients undergoing cardiac surgical procedures utilizing sufentanil (plasma concentrations ranging from 3–55 ng/ml). Their results thus parallel the observations made in the present study in dogs.

Second, Stanley et al.\textsuperscript{22} observed that lofentanil anesthesia in rats was associated with a 30% occupancy of the total opioid receptors in brain.\textsuperscript{22} Varying distribution of opioid receptors has been demonstrated by Maurer in the rat, human, guinea pig, and pig.\textsuperscript{23} It may be that the dog was fewer opioid receptors which become saturated at the concentrations achieved in this study. Further increments in plasma sufentanil would,
TABLE 5. Heart Rate and Blood Pressure Responses to Tail-clamp at Each Infusion Rate

<table>
<thead>
<tr>
<th>Maintenance Infusion Rate (μg·kg⁻¹·min⁻¹)</th>
<th>N‡</th>
<th>O‡</th>
<th>Heart Rate (bpm)§</th>
<th>Increase with Movement (bpm)</th>
<th>Increase with No Movement (bpm)</th>
<th>Mean Aortic Pressure (mmHg) ‡</th>
<th>Increase with Movement (mmHg)</th>
<th>Increase with No Movement (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25</td>
<td>81</td>
<td>115 ± 3</td>
<td>11 ± 4</td>
<td>73 ± 2</td>
<td>9 ± 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.005</td>
<td>18</td>
<td>133</td>
<td>85 ± 5**</td>
<td>20 ± 5</td>
<td>12 ± 2</td>
<td>18 ± 3</td>
<td>13 ± 2</td>
<td></td>
</tr>
<tr>
<td>0.015</td>
<td>6</td>
<td>21</td>
<td>63 ± 4***</td>
<td>14 ± 3</td>
<td>13 ± 3</td>
<td>18 ± 4</td>
<td>16 ± 2</td>
<td></td>
</tr>
<tr>
<td>0.045</td>
<td>4</td>
<td>12</td>
<td>54 ± 3**</td>
<td>14 ± 3</td>
<td>10 ± 6</td>
<td>18 ± 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.405</td>
<td>4</td>
<td>12</td>
<td>49 ± 6**†</td>
<td>14 ± 4</td>
<td>3 ± 7</td>
<td>28 ± 2</td>
<td>13 ± 6</td>
<td></td>
</tr>
<tr>
<td>1.215</td>
<td>10</td>
<td>102</td>
<td>60 ± 5**†</td>
<td>10 ± 2</td>
<td>5 ± 1</td>
<td>23 ± 5</td>
<td>16 ± 8</td>
<td></td>
</tr>
</tbody>
</table>

There were no statistically significant differences among the hemodynamic responses produced when application of the tail-clamp produced movement vs. no movement.

* Values represent mean ± SEM
† Total number of dogs studied at the indicated maintenance infusion rate.
‡ Total number of observations of movement or lack thereof to the tail-clamp stimulus.
§ Hemodynamic variable measured just before beginning the determination of enflurane MAC during each of the maintenance sufentanil infusion rates listed in column 1.
† P < 0.05 vs. control.
** P < 0.05 vs. 0.005 μg·kg⁻¹·min⁻¹.
†† P < 0.05 vs. 0.015 μg·kg⁻¹·min⁻¹.

therefore, not produce any further increase in MAC reduction. This would explain in part the observed species differences. However, the species differences may be more apparent than real.

Examination of the plasma concentrations required to produce maximum anesthetic efficacy of the opioids reveals remarkable similarity between humans and dogs. Sprigge et al. found plasma fentanyl levels of 15 ng/ml to approximate the EC₅₀ (concentration necessary to produce an effect in 50% of subjects) for suppression of hemodynamic responses to different noxious stimuli in patients having cardiac surgery. From examination of their data, it appears that plasma levels of 30 ng/ml would approximate the EC₅₀ (concentration necessary to produce an effect in 90% of subjects). In the dog, plasma fentanyl concentrations of approximately 5 ng/ml reduced enflurane MAC by 50%, and concentrations between 10 and 30 ng/ml were associated with near maximum achievable reduction (57–64%) of enflurane MAC. Arndt et al. have also demonstrated in awake, trained dogs that the maximum effectiveness of fentanyl in terms of its obliteration of hemodynamic and somatic responses to tail-clamp stimulation occurred at plasma fentanyl concentrations of 30 ng/ml. The similarity between the sufentanil plasma concentration-effect relationship in humans and that reported in this study in dogs has been noted above. The similarity between concentration-effect relationships in humans and animals is not unique to the opioids. Indeed, there is remarkable similarity between animals and humans in the values described for MAC for the volatile anesthetics. These relationships suggest that, rather than focusing on dose-effect relationships when comparing species differences, a more appropriate comparison would be the plasma concentration versus effect relationships.

In regard to the relative potency of sufentanil compared to fentanyl, it is interesting to note that 1) the potency ratio based on dosage is 5–10, with most observations centering around 7; 2) the potency ratio based on plasma concentrations required for a 50% reduction of enflurane MAC is approximately 7 (i.e., 0.7 ng/ml for sufentanil versus 5 ng/ml for fentanyl); and 3) the physicochemical properties (including ionization, lipid solubility, and binding to plasma proteins at pH 7.40) of sufentanil and fentanyl are such that the two opioids can be expected to have similar degrees of access to opioid receptors in the brain. Thus, similarities between potency ratios based on equivalent doses and on equivalent plasma concentrations are not surprising.

Complete anesthesia in human patients has been reported only for large doses of fentanyl or sufentanil combined with some other CNS depressant (e.g., hypnotic or minor tranquilizer administered either as premedication or as an anesthetic supplement). Also, most patients receiving narcotics as the "sole" anesthetic are paralyzed, and this precludes the possibility of observing somatic responses to noxious stimuli as indicators of inadequate anesthesia (thus, perhaps contributing to the incidence of awareness under anesthesia).

A lack of hemodynamic responses to noxious stimulation is not necessarily indicative of a depth of anesthesia sufficient to obtund somatic responses. Stimulation by tail-clamp produced nearly equivalent increases of heart rate and blood pressure whether the animals moved or not. These findings indicate that hemodynamic and somatic signs are not interchangeable as indicators of an-

esthetic depth. We and others have consistently observed patient movement, even eye opening, with strong stimulation (e.g., electrocautery, sternotomy) that failed to elicit any change in hemodynamics nor any other evidence of sympathetic activity.30,31++

In this study, the degree of enflurane MAC reduction was the same when the plasma concentration (approximately 50 ng/ml) was achieved in the first hour or after several hours of progressively increasing priming and maintenance infusions (78.0 versus 70.5%).

This study addressed the question of stability of enflurane MAC reduction by opioids over time. Murphy and Hug previously demonstrated that enflurane MAC was stable over time in the absence of an opioid.6 In the present study, however, there was a significant decline in the degree of MAC reduction in some dogs when stable low plasma sufentanil levels were maintained for several hours (group 2; fig. 3). The basis for this progressively decreasing effectiveness despite stable sufentanil concentrations is unknown, but the following points should be considered. It may be that CNS tolerance developed over the 7-h period of observation in the low-dose group. Tolerance to moderate doses of opioids has been demonstrated to develop acutely (within hours) in animals (including dogs32,33) and humans.34-36 The development of tolerance may not have been as evident in the high-dose group because the period of observation was short and the plasma concentrations used much higher than those required to produce the maximum reduction of enflurane MAC. Tolerance to opioids is never absolute, and can be overcome by sufficiently large doses.36 In the high-dose group, tolerance development in the 7-h period of observation may not have occurred to the degree necessary to reduce the effectiveness of the high plasma concentrations below that required for the maximum reduction of enflurane MAC. In other words, the low-dose group (group 2) was on the steep portion of the sufentanil concentration versus MAC reduction curve, where small to moderate changes in the effectiveness of the opioid would be most evident. The high-dose group (group 3) was far out on the plateau of the concentration versus response curve. Askiopoulos et al. have also demonstrated the rapid development of tolerance to moderate doses of fentanyl in the suppression of hemodynamic responses to sensory nerve stimulation in the dog. Differences in experimental design prevent direct comparisons between their data and ours.32

In summary, this study demonstrated a ceiling effect to MAC reduction by sufentanil in dogs of approximately 70%. The maximum reduction occurred with relatively low dose rates, and did not increase significantly even when massive doses were administered. The degree of MAC reduction was independent of the dose-rate at which it was achieved. The degree of MAC reduction was fairly constant over several hours when supramaximal plasma levels of sufentanil were maintained. Acute tolerance to sufentanil's reduction of enflurane MAC was evident in one-half of the dogs in which moderate plasma concentrations of sufentanil were maintained for 4–8 h.

References

17. Gilbert PE, Martin WR: The effects of morphine-like drugs in the nondependent, morphine-dependent,
and cytochrome-dependent chronic spinal dog. J Pharmacol Exp Ther 198:66–82, 1976