Effect of remifentanil hydrochloride administered via constant rate infusion on the minimum alveolar concentration of isoflurane in cats

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Objective—To evaluate the effects of increasing doses of remifentanil hydrochloride administered via constant rate infusion (CRI) on the minimum alveolar concentration (MAC) of isoflurane in cats.

Animals—6 healthy adult cats.

Procedures—For each cat, 2 experiments were performed (2-week interval). On each study day, anesthesia was induced and maintained with isoflurane; a catheter was placed in a cephalic vein for the administration of lactated Ringer’s solution or remifentanil CRIs, and a catheter was placed in the jugular vein for collection of blood samples for blood gas analyses. On the first study day, individual basal MAC (MAC_{Basal}) was determined for each cat. On the second study day, 3 remifentanil CRIs (0.25, 0.5, and 1.0 µg/kg/min) were administered (in ascending order); for each infusion, at least 30 minutes elapsed before determination of MAC (designated as MAC_{R0.25}, MAC_{R0.5}, and MAC_{R1.0}, respectively). A 15-minute washout period was allowed between CRIs. A control MAC (MAC_{Control}) was determined after the last remifentanil infusion.

Results—Mean ± SD MAC_{Basal} and MAC_{Control} values at sea level did not differ significantly (1.66 ± 0.08% and 1.52 ± 0.21%, respectively). The MAC values determined for each remifentanil CRI did not differ significantly. However, MAC_{R0.25}, MAC_{R0.5}, and MAC_{R1.0} were significantly decreased, compared with MAC_{Basal}, by 23.4 ± 7.9%, 29.8 ± 8.3%, and 26.0 ± 9.4%, respectively.

Conclusions and Clinical Relevance—The 3 doses of remifentanil administered via CRI resulted in a similar degree of isoflurane MAC reduction in adult cats, indicating that a ceiling effect was achieved following administration of the lowest dose. (Am J Vet Res 2009;70:581–588)
we hypothesized that increasing doses of remifentanil anesthetics in dogs, rats, and humans. The MAC-sparing effects of different opioids for inhalant anesthetics have been quantified in several species.6–10

Opioids are commonly administered in combination with inhalant anesthetics, as part of balanced techniques, with the aims of reducing the concentration of an inhalant anesthetic that is required to effectively and safely achieve anesthesia and providing better hemodynamic stability by partial or complete suppression of autonomic (sympathetic nervous system stimulation) and somatic (motor and sensory) responses induced by noxious stimuli.21 In studies22,23 in cats, IV administration of alfentanil induced a 35% reduction in isoflurane MAC, which resulted in an improvement of cardiovascular function, compared with the effect of isoflurane alone. Intravenous administration of other opioids to cats (including morphine, buprenorphine, butorphanol, and U50488H) and transdermal administration of fentanyl were associated with reductions in isoflurane MAC of 11% to 28%.10,20 Remifentanil hydrochloride, a phenylpiperidine opioid derivative that has been recently introduced for clinical use, has potent analgesic property as a result of its agonistic action against opioid OF3 (mu) receptors.23 Remifentanil contains an ester linkage in the molecular structure that makes it susceptible to metabolism by nonspecific plasma and tissue esterases24; thus, remifentanil effects are short lasting, and recovery from those effects is rapid because of a substantially small context-sensitive half-time (time required for the plasma concentration to decrease by 50% after termination of an infusion regimen) that is independent of the duration of a CRI. Therefore, remifentanil is considered the ideal drug for use as a CRI because of lack of cumulative effects even after prolonged infusions.25,26,30–32 With regard to anesthesia of cats, the differential biotransformation of remifentanil is of special interest because of the deficiency of hepatic metabolism in some pathways in this species.27–30 The pharmacokinetics of remifentanil remain unchanged in humans with severe liver and renal impairment,30,31 which could represent an advantage in feline patients that have similar clinical conditions. The pharmacokinetic characteristics of remifentanil in cats32 (ie, rapid distribution from the central [bloodstream] to peripheral compartments and high clearance) are similar to those in humans and dogs.23,33 Therefore, similar rapid onset and offset of effects are expected,32 which may facilitate titration of effects to avoid development of signs of CNS excitation that are commonly associated with opioids in cats.

Constant rate infusion of remifentanil in association with administration of inhalant anesthetic agents could be a potential balanced anesthesia technique in cats. Remifentanil CRI has resulted in significant dose-dependent reductions in MAC of different inhalant anesthetics in dogs, rats, and humans.8,11,12 Therefore, we hypothesized that increasing doses of remifentanil administered consecutively via CRI would decrease the MAC of isoflurane in cats in a dose-dependent fashion. Because remifentanil is expected to be rapidly eliminated in cats,23 we also hypothesized that the MAC values of isoflurane determined after the end of the series of remifentanil CRIs would rapidly return to basal MAC values recorded before initiation of opioid infusions.

**Materials and Methods**

**Animals**—Six adult (3- to 7-year-old) neutered mixed-breed cats (4 females and 2 males) were assigned to the study, after approval by the Institutional Animal Care Committee (protocol No. 124/2005-CEEA). Mean ± SD weight of the cats was 3.9 ± 0.5 kg. Before commencement of the study, all cats were vaccinated, de-wormed, and assessed as clinically normal on the basis of results of a physical examination, serum biochemical analyses, and a CBC. In addition, PCR testing for FeLV and FIV was performed to ensure that all cats included in the study were negative for those infections. Cats were group housed in a large room (in accordance with established standards30), provided with fresh water ad libitum, and fed a commercial dry cat food with supplemental canned food provided periodically.

**Anesthesia and instrumentation**—Twelve hours prior to each of the 2 study days, each cat was weighed and moved to a single cage in a quiet environment; food was withheld, but water was provided. For induction of anesthesia, the cat was placed in an acrylic chamber into which 5% isoflurane in 100% oxygen (5 L/min) was delivered with a calibrated out-of-circuit vaporizer and a pediatric circle circuit. The time required for chamber induction (ie, loss of spontaneous movement) was recorded in each study day. Subsequently, the cat was removed from the chamber, and isoflurane was administered via face mask until orotracheal intubation with auffed endotracheal tube could be achieved. Thereafter, the cat was positioned in lateral recumbency and mechanically ventilated (pressure-controlled mode) with respiratory rate and inspiratory peak airway pressure adjusted to maintain PetCO2 and ETCO2 values at 30 to 40 mm Hg throughout the anesthetic episode. A thin plastic catheter was placed through the lumen of the endotracheal tube so that the tip was at the distal end of the tube within the thoracic trachea; the other end, which exited at the connection of the endotracheal tube with the breathing circuit, was connected to a side-stream infrared gas analyzer4 for continuous measurements of ETCO2 and ET50%. The analyzer was calibrated with a reference sample provided by the manufacturer at the beginning and midpoint of each study day procedures.

After induction of anesthesia in each cat, the instrumentation phase was completed in approximately 30 minutes while ET50% was maintained between 2.0% and 2.3%. A 24-gauge catheter was inserted in a cephalic vein for administration of lactated Ringer's solution by use of a peristaltic pump or remifentanil hydrochloride CRI (0.25, 0.5, and 1.0 μg/kg/min) diluted with saline (0.9% NaCl) solution by use of a syringe pump. All infusions were delivered at rate of 3 mL/kg/h; the infusion of lactated Ringer's solution started after place-
ment of the catheter and was substituted with remifentanil during the respective CRI for the duration of the infusion. A jugular vein was percutaneously catheterized with a 20-gauge catheter for collection of venous blood samples in heparinized syringes for measurement of venous blood pH, P\textsubscript{a}CO\textsubscript{2}, and bicarbonate concentration by use of a blood gas analyzer\cite{1} with correction for body temperature (°C).\cite{2} A thermometer was advanced to the thoracic portion of the esophagus for monitoring of body temperature, which was maintained at 37.5° to 38.5°C by use of a forced warm-air blanket.\cite{3} A lead II ECG\cite{4} was used to continuously monitor heart rate and rhythm. To determine SAP, an ultrasonographic Doppler flow probe was placed over the caudal branch of a saphenous artery with an occluding cuff (width, 40% of the limb circumference) placed above the tarsal joint. A pulse oximeter probe\cite{5} was placed on the tongue for arterial \textsuperscript{2}O\textsubscript{2} monitoring.

**MAC determination**—Determinations of MAC were completed by use of a previously described technique.\cite{6} A supramaximal noxious stimulus was applied by means of two 24-gauge stainless steel needles that were positioned subcutaneously 3 cm apart in the middle third of an antebrachium. The needles were connected to an electrical stimulator\cite{7} (50 V; 50 cycles/s; pulse duration, 10 milliseconds). The pattern of electrical stimulation consisted of a sequence of 4 stimuli at 5-second intervals: 2 single stimuli were followed by 2 stimuli that were each continuously applied for 3 seconds. The whole sequence of nociceptive stimulation was completed unless a positive motor response was observed during the process. A positive motor response was defined as a gross purposeful movement of head or limbs, with the exception of the forelimb that underwent electrical stimulation. A negative response included the lack of movement of head and limbs, muscle rigidity, shivering, tail movement, coughing, swallowing, or an increase in spontaneous respiratory efforts during controlled ventilation.

After instrumentation of each cat and a period of equilibration of at least 15 minutes at an ET\textsubscript{ISO} of 1.8% to 2.2% (similar to reported values of isoflurane MAC in cats\cite{8-10,11-13}), ET\textsubscript{ISO} was increased or decreased by 0.1% after a positive or negative response, respectively, was obtained. The ET\textsubscript{ISO} was kept constant for at least 15 minutes at each set value before delivery of the electrical stimulus, and the process of increasing or decreasing concentrations was repeated until a positive response was followed by a negative response or vice versa. The MAC was calculated as the mean of 2 successive ET\textsubscript{ISO} values associated with 1 positive and 1 negative response. Minimum alveolar concentration values were corrected to sea level by use of a formula as follows: (barometric pressure of location/760 mm Hg) × obtained MAC value. The mean barometric pressure obtained from the official city meteorologic station for the altitude at which the experiment was completed (ie, 785 m above sea level) corresponded to 680 mm Hg.

**Experimental protocol**—Each cat was anesthetized 2 times; there was an interval of at least 2 weeks between the anesthetic procedures. The study was designed so that each cat acted as its own control animal. On the first study day, MAC\textsubscript{Basal} was determined. On the second study day, isoflurane MAC was recorded during administrations of 3 CRIs of remifentanil; 0.25, 0.5, and 1.0 µg of remifentanil/kg/min were each administered (in ascending order) without a loading dose. Each remifentanil CRI was maintained for 30 minutes before the first stimulus was applied. After each MAC determination, the remifentanil CRI was discontinued and lactated Ringer’s solution (3 mL/kg/h) was infused for 15 minutes before the beginning of the next CRI. After the last MAC determination (ie, determination of MAC\textsubscript{R0.25}), MAC\textsubscript{Control} was determined after a 15-minute washout period to verify whether isoflurane MAC had returned to the values recorded during baseline conditions (ie, MAC\textsubscript{Basal}). During the interval after MAC\textsubscript{R0.5} determination and before MAC\textsubscript{R1.0} determination, the needle electrodes used for nociceptive stimulation were repositioned 1 cm from their previous locations (maintaining a distance of 3 cm between them) to avoid local desensitization.\cite{14}

The duration of each MAC determination (MAC\textsubscript{Basal}, MAC\textsubscript{R0.25}, MAC\textsubscript{R0.5}, MAC\textsubscript{R1.0}, and MAC\textsubscript{Control}) on both study days was recorded and considered the time from the beginning of the ET\textsubscript{ISO} equilibration period to the last electric stimulus applied to obtain the MAC value. The duration of each remifentanil CRI was also recorded. On both study days, cardiopulmonary and blood gas analysis data were collected immediately before application of each noxious stimulus, values corresponding to each MAC level were calculated as the arithmetic mean of the value obtained at the negative and positive response.

After the final MAC determination on either study day (ie, MAC\textsubscript{Equal} or MAC\textsubscript{Control}), all catheters were removed and meloxicam\cite{15} (0.2 mg/kg, SC) was administered; isoflurane administration was discontinued, and the time to extubation, determined by the presence of palpebral reflex and resumption of normal ventilation, was recorded. On the second study day (the remifentanil treatment day), the time to walking with ataxia and time to complete recovery (ie, apparently normal ambulation), determined from the time of extubation, were also recorded.

**Statistical analysis**—An ANOVA for repeated measurements was used to compare MAC, heart rate, inspiratory peak airway pressure, P\textsubscript{a}CO\sub{2}, venous blood pH and bicarbonate concentration, and ET\textsubscript{CO}\textsub{2} values obtained in the 3 experiments (ie, the values recorded on the first study day [basal values] and on the second study day [values for the 3 remifentanil CRIs and control values]). To compare variables such as esophageal temperature, SAP, respiratory rate, \textsuperscript{2}O\textsubscript{2} saturation, and durations of MAC determination and remifentanil CRIs, a Friedman test was used. Differences were considered significant at a value of P < 0.05. A Shapiro-Wilk test was used for assessment of data normality, and a Levene test was used for the assessment of variables’ variance equality among the experiments. Thus, for variables for which normality was not rejected, data were analyzed via an ANOVA and findings are expressed as mean ± SD. Alternatively, a Friedman test was used, and results are expressed as median (lower quartile to upper quartile). Comparisons among basal, remifentanil CRIs, and con-
Results

Determinations of MAC and assessments of cardiopulmonary and blood gas variables were completed successfully for all cats in the present study. Values of MAC\textsubscript{baseline} and MAC\textsubscript{control} were not significantly different (Table 1). Mean value of isoflurane MAC during each remifentanil CRI was significantly lower than MAC\textsubscript{baseline}; however, there was no significant difference among the MAC\textsubscript{R0.25}, MAC\textsubscript{R0.5}, and MAC\textsubscript{R1.0} values and no significant difference between each of those values and MAC\textsubscript{control}. Times for all MAC determinations were similar.

Unlike findings for the other assessed variables, the effect of remifentanil infusions on P\textsubscript{vCO\textsubscript{2}} and SAP was significant (Table 2). During the 1.0 µg/kg/min infusion of remifentanil, SAP was significantly increased, compared with the value during the control experiment. During the 0.5 µg/kg/min infusion of remifentanil, P\textsubscript{vCO\textsubscript{2}} was significantly decreased, compared

Table 1—Minimum alveolar concentration of isoflurane assessed before (baseline; MAC\textsubscript{baseline}) was assessed on the first study day and during administration of 3 consecutive CRIs of remifentanil hydrochloride (0.25, 0.5, and 1.0 µg/kg/min; assessed 2 weeks later on the second study day) in 6 cats; MAC\textsubscript{control} was determined after cessation of the last remifentanil CRI. The time required to complete each MAC determination was recorded. For each experimental condition, the percentage of MAC reduction from the MAC\textsubscript{baseline} value was calculated.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>0.25</th>
<th>0.5</th>
<th>1.0</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC (%)</td>
<td>1.66 ± 0.08\textsuperscript{a}</td>
<td>1.27 ± 0.13\textsuperscript{a}</td>
<td>1.16 ± 0.17\textsuperscript{a}</td>
<td>1.22 ± 0.15\textsuperscript{a}</td>
<td>1.52 ± 0.21\textsuperscript{a}</td>
</tr>
<tr>
<td>MAC reduction (%)</td>
<td>NA</td>
<td>23.4 ± 7.9</td>
<td>29.8 ± 6.3</td>
<td>26.0 ± 9.4</td>
<td>8.1 ± 11.8</td>
</tr>
<tr>
<td>Time for MAC determination (min)</td>
<td>77 ± 27</td>
<td>56 ± 13</td>
<td>48 ± 21</td>
<td>42 ± 10</td>
<td>69 ± 38</td>
</tr>
</tbody>
</table>

Values for MAC and MAC reduction (normal distribution) are reported as mean ± SD on a log scale. Time for MAC determination (values where the hypothesis of normal data distribution was rejected [P < 0.05]) are reported as mean ± SD and median (lower quartile to upper quartile range).

NA = Not applicable.

\textsuperscript{a}Within a row, values with different superscript letters are significantly (P < 0.05) different. Comparisons among the baseline, remifentanil CRIs, and control data were based on the CI for the mean (95% CI) or the median (96.9% CI). For the MAC comparisons, the CIs were as follows: baseline, 1.57% to 1.74%; 0.25 µg of remifentanil/kg/min, 1.13% to 1.41%; 0.5 µg of remifentanil/kg/min, 0.99% to 1.34%; 1.0 µg of remifentanil/kg/min, 1.08% to 1.38%; and control, 1.30% to 1.74%.

Table 2—Physiologic variables recorded during isoflurane MAC determination before (baseline) and during administration of 3 consecutive CRIs of remifentanil (0.25, 0.5, and 1.0 µg/kg/min; assessed 2 weeks later on the second study day) in 6 cats; a control experiment was conducted after the last remifentanil CRI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>0.25</th>
<th>0.5</th>
<th>1.0</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>168 ± 26\textsuperscript{a}</td>
<td>204 ± 42\textsuperscript{a}</td>
<td>213 ± 24\textsuperscript{a}</td>
<td>195 ± 20\textsuperscript{a}</td>
<td>182 ± 13\textsuperscript{a}</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>136 ± 33</td>
<td>160 ± 26</td>
<td>167 ± 28</td>
<td>168 ± 17</td>
<td>131 ± 17</td>
</tr>
<tr>
<td>Esophageal temperature (°C)</td>
<td>38.2 ± 0.3</td>
<td>38.0 (37.9–38.2)</td>
<td>38.0 (37.9–38.2)</td>
<td>38.4 (38.2–38.5)</td>
<td>38.1 (38.0–38.3)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>17 ± 1</td>
<td>19 ± 4</td>
<td>22 ± 3</td>
<td>22 ± 3</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>P\textsubscript{awt} (cm H\textsubscript{2}O)</td>
<td>17 (16–18)\textsuperscript{a}</td>
<td>19 (15–24)\textsuperscript{a}</td>
<td>22 (19–23)\textsuperscript{a}</td>
<td>23 (19–24)\textsuperscript{a}</td>
<td>23 (14–23)\textsuperscript{a}</td>
</tr>
<tr>
<td>ETCO\textsubscript{2} (mm Hg)</td>
<td>32.8 ± 2.1\textsuperscript{a}</td>
<td>32.2 ± 3.6\textsuperscript{a}</td>
<td>31.9 ± 2.9\textsuperscript{a}</td>
<td>35.2 ± 3.4\textsuperscript{a}</td>
<td>31.8 ± 3.3\textsuperscript{a}</td>
</tr>
<tr>
<td>P\textsubscript{vCO\textsubscript{2}} (mm Hg)</td>
<td>34.5 ± 4.7\textsuperscript{a}</td>
<td>34.5 ± 3.5\textsuperscript{a}</td>
<td>32.7 ± 1.2\textsuperscript{a}</td>
<td>37.5 ± 2.4\textsuperscript{a}</td>
<td>32.5 ± 4.8\textsuperscript{a}</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.10\textsuperscript{a}</td>
<td>7.36 ± 0.04\textsuperscript{a}</td>
<td>7.36 ± 0.03\textsuperscript{a}</td>
<td>7.30 ± 0.04\textsuperscript{a}</td>
<td>7.37 ± 0.05\textsuperscript{a}</td>
</tr>
<tr>
<td>HCO\textsubscript{3} (mmol/L)</td>
<td>19.3 ± 1.8 \textsuperscript{a}</td>
<td>20.3 ± 1.9 \textsuperscript{a}</td>
<td>19.1 ± 1.5 \textsuperscript{a}</td>
<td>18.4 ± 1.7 \textsuperscript{a}</td>
<td>19.8 ± 1.3 \textsuperscript{a}</td>
</tr>
<tr>
<td>SpO\textsubscript{2} (%)</td>
<td>99.3 ± 0.4</td>
<td>99.3 ± 0.6</td>
<td>99.1 ± 0.6</td>
<td>99.3 ± 0.8</td>
<td>99.5 ± 0.5</td>
</tr>
<tr>
<td>P\textsubscript{awt} = Inspiratory peak airway pressure. HCO\textsubscript{3} = Venous blood bicarbonate concentration.</td>
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</table>

Values with normal distribution are reported as mean ± SD only. Values for which the hypothesis of normal distribution was rejected (P < 0.05) are reported as mean ± SD and median (lower quartile to upper quartile range).

Within a row, mean or median values with different superscript letters are significantly (P < 0.05) different. Comparisons among the baseline, remifentanil CRIs, and control data were based on the CI for the mean (95% CI) or the median (96.9% CI). For comparisons of SAP, the CIs were as follows: baseline, 108 to 181 mm Hg; 0.25 µg of remifentanil/kg/min, 131 to 200 mm Hg; 0.5 µg of remifentanil/kg/min, 153 to 201 mm Hg and control, 106 to 148 mm Hg. For comparisons of P\textsubscript{vCO\textsubscript{2}}, the CIs were as follows: baseline, 29.5 to 39.4 mm Hg; 0.25 µg of remifentanil/kg/min, 30.8 to 38.2 mm Hg; 0.5 µg of remifentanil/kg/min, 31.4 to 33.9 mm Hg; 1.0 µg of remifentanil/kg/min, 35.1 to 40.0 mm Hg and control, 27.5 to 37.6 mm Hg.)
with the value during the 1.0 µg/kg/min infusion of remifentanil.

Time for induction of anesthesia with isoflurane was 7.6 ± 1 minutes and 7 ± 2 minutes for the first and second study days, respectively, with additional 3 ± 1 minutes of isoflurane administration via face mask on both study days. On the second study day, the durations of remifentanil administrations were not significantly different among the 3 CRI rates (Table 3).

Three of the 6 cats during the first study day (isoflurane alone) and 4 of the 6 cats during the second study day (isoflurane and remifentanil) had a rough recovery from anesthesia, characterized by thrashing and paddling inside the cage for a few minutes at the time of extubation, after which they all became calm. Isoflurane administration was discontinued 14.3 ± 8 minutes and 14.5 ± 2 minutes, respectively, after the last MAC determination (MAC_{Baseline} and MAC_{Completion}) in each study day. Time to extubation was 1.7 ± 1.2 minutes and 1.5 ± 0.5 minutes for the first and second study days, respectively. On the second study day, time to walking with ataxia and time to complete recovery (ie, apparently normal ambulation) were 12.4 ± 1.5 minutes and 24.5 ± 5.2 minutes, respectively.

### Discussion

Constant rate infusions of remifentanil cause a maximum isoflurane MAC decrease of 65% and 91% in rats and humans, respectively.\(^{11,15}\) In dogs that received remifentanil via CRI, enflurane MAC was decreased by approximately 63% and the dose estimated to cause a 50% reduction was 0.72 µg/kg/min.\(^{9}\) However, in a clinical study,\(^{40}\) infusions of remifentanil at rates of 0.1 and 0.25 µg/kg/min in dogs decreased isoflurane requirements in a dose-dependent manner by as much as 50% during orthopedic procedures. The MAC_{Baseline} in the cats of the present study (1.66%) was similar to values determined in other studies\(^{9,10,20,36,41}\) for this species, although reported values range from 1.2% to 2.2%. The percentage MAC reduction (compared with MAC_{Baseline}) attributable to remifentanil in cats in the present study (23% to 30% for the 3 remifentanil CRIs) was less than the percentage MAC reductions reported for other species.\(^{8,11,15}\) However, the percentage MAC reduction among the 3 CRI doses was similar, despite administration of doses in ascending order on the same study day. Opioid-induced MAC reductions in horses, swine, and cats are of less magnitude than those in dogs, rats, monkeys, and humans.\(^{7,9,13,16-19,42}\)

Doses selected for investigation in the present study were based on remifentanil infusion rates of 0.2 to 0.23 µg/kg/min that, when combined with propofol (0.3 mg/kg/min), appear to provide adequate clinical anesthesia in cats undergoing ovariohysterectomy.\(^{11}\) Three doses were investigated: 0.25, 0.5, and 1.0 µg of remifentanil/kg/min. The lowest dose was used in the aforementioned clinical study\(^{8}\); the 0.5 and 1.0 µg/kg/min CRIs were included to determine whether a ceiling effect could be achieved because a study\(^{9}\) in dogs revealed a ceiling enflurane MAC reduction (63%) at a CRI of 1.0 µg of remifentanil/kg/min.

Ceiling effects for MAC reduction induced by the phenylpiperidine opioid derivatives fentanyl,\(^{16,17}\) sufentanil,\(^{6,13}\) alfentanil,\(^{7,9}\) and remifentanil\(^{8}\) have been reported. In the present study, a 4-fold difference in the CRI dose of remifentanil (0.25 vs 1.0 µg/kg/min) did not affect the degree of MAC reduction, indicating that a ceiling isoflurane-sparing effect was already achieved with the lower CRI. On the basis of findings of the present study, the specific infusion rate at which this ceiling effect is achieved in cats cannot be determined.

The value of MAC_{Completion} (determined after cessation of high-dose CRI and subsequent 15-minute washout period) was not significantly different from MAC_{Baseline}, MAC_{Completion}, or MAC_{Baseline}. In our study, MAC_{Completion} was determined to ensure that MAC had returned to baseline value after completion of all 3 remifentanil CRIs; if MAC_{Completion} differed significantly from MAC_{Baseline}, then likely a cumulative effect of repeated infusions of remifentanil had developed or a modified response to the repeated electrical stimulation during MAC determinations had occurred. With regard to a cumulative drug effect, the elimination half-life of remifentanil must be considered. The elimination half-life of remifentanil in isoflurane-anesthetized cats is 15.7 minutes,\(^{12}\) which is longer than the value in dogs (5.6 minutes)\(^{39}\) and similar to the value in humans (10 to 20 minutes).\(^{20,44}\) The relatively short elimination half-life of remifentanil in cats\(^{32}\) suggests that this drug would be rapidly eliminated after a prolonged infusion regimen, such as the one used in the present study. However, elimination half-life has little value for describing the disposition of drugs, such as remifentanil, that are administered via CRI because of the multicompartiment model.\(^{45,46}\) The context-sensi-

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**Table 3—Duration of infusion and total amount of remifentanil administrated via each of the 3 consecutive CRIs (0.25, 0.5, and 1.0 µg of remifentanil/kg/min) in 6 isoflurane-anesthetized cats during experiments to evaluate the MAC-sparing effects of the phenylpiperidine opioid derivative.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Remifentanil CRI (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>73.7 ± 14.2</td>
</tr>
<tr>
<td>Amount of remifentanil administered (µg)</td>
<td>73.1 ± 11.6</td>
</tr>
<tr>
<td>Values are reported as mean ± SD and median (lower quartile to upper quartile). The duration of each CRI did not differ significantly.</td>
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</tr>
</tbody>
</table>
tive half-time, defined as the time required for plasma concentration to decrease 50% after termination of an infusion designed to maintain a constant concentration. It incorporates the multicompartmental behavior of drugs following IV administration and better reflects the rapidity of drug elimination during the course of prolonged IV infusion regimens. Remifentanil’s context-sensitive half-time, determined to date only in humans, is extremely short (approx 3 minutes) and is independent of the duration of the infusion, indicating that this drug has no cumulative effects in humans. In a study in dogs, the enflurane MAC determined 30 minutes after discontinuation of a CRI of remifentanil was no different from the pretreatment baseline MAC value, indicating no cumulative drug effect for this species. It is possible that the longer half-life of remifentanil in cats results in a cumulative effect because the MAC<sub>final</sub> value in our study was not significantly different from MAC<sub>R0.25</sub>, MAC<sub>R0.5</sub>, or MAC<sub>R1.0</sub> even though assessment of MAC<sub>final</sub> was started at a 15-minute washout period and the median time to MAC determination was 55 minutes. Because a ceiling effect was achieved for MAC values associated with the 3 CRI doses, it is also possible that all doses were high and facilitated the cumulative effect, which did not allow for complete return to MAC<sub>baseline</sub> value at the end of the second study day.

Albeit a nonsignificant difference, MAC<sub>final</sub> was 0.1% to 0.4% lower than MAC<sub>baseline</sub> in 4 of the 6 cats in the present study. This could be explained by a modification in the motor response as a result of repeated noxious stimulation. Desensitization of the skin caused by repeated electrical stimulation has been reported as a cause of a type II error (ie, a false-negative result) and also rules out the influence of a small sample size in our study. This CNS-stimulating effect can minimize the MAC-sparing effect of opioids and may result in increased sympathetic nervous system activity. This CNS-stimulating effect can minimize the MAC-sparing effect of opioids and may result in increased sympathetic nervous system activity. Finally, the use of lower ET<sub>30</sub> during remifentanil CRIs also resulted in less cardiovascular depression and less effect on measured variables.

For the cats in our study, the time to recovery from isoflurane anesthesia was similar to that reported by other authors. The observed characteristics of anesthetic recovery were probably attributable to residual isoflurane effects and were not associated with the use of remifentanil. The excitement observed in 4 of 6 cats during recovery from isoflurane-remifentanil anesthesia was also evident during the recovery phase in some of those cats (3/6) when they were anesthetized with isoflurane alone.

Results of the present study indicated that CRI of remifentanil reduced the isoflurane MAC in cats, with a ceiling effect at the tested doses, and that no major cardiovascular effects developed in association with these infusion protocols. On the basis of these findings and considering the doses evaluated, remifentanil CRIs at rates > 0.25 µg/kg/min did not achieve increasingly higher MAC reductions; however, whether CRIs at rates < 0.25 µg/kg/min could result in a comparable MAC reduction was not determined in our study. Further clinical and experimental studies involving a greater number of cats and lower doses of remifentanil administered via CRI are recommended to determine the optimal CRI dose of remifentanil for MAC reduction in isoflurane-anesthetized cats.

a. Isoflurane, Cristália, Itapira, SP, Brazil.
b. Inter VPZ ISO, Intermed, São Paulo, SP, Brazil.
c. Inter Linea C, Intermed, São Paulo, SP, Brazil.
d. Gas analyzer module G-AO A/S 3 monitor, Datex-Engstrom, Helsinki, Finland.
e. Quick Cal calibration gas, Datex-Engstrom, Helsinki, Finland.
f. Peristaltic infusion pump ST 530 T2, Samtronic Infusion Systems, Sorocoro, SP, Brazil.
g. Ultiva (1 mg), Glaxo Welcome SA, Rio de Janeiro, RJ, Brazil.
h. Syring infusion pump ST 680, Samtronic Infusion Systems, Sorocoro, SP, Brazil.
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