Anesthetic Potency of Remifentanil in Dogs

Luis G. Michelsen, M.D.,* Markku Salmenperä, M.D.,† Carl C. Hug, Jr., M.D., Ph.D.,‡ Fania Szlam, M.M.Sc.,§
Dirk VanderMeer, M.D. †

Background: Remifentanil is an opioid that is rapidly inactivated by esterases in blood and tissues. This study examined the anesthetic potency and efficacy of remifentanil in terms of its reduction of enflurane minimum alveolar concentration (MAC) in dogs.

Methods: Twenty-five dogs were anesthetized with enflurane. One group received incremental infusion rates of remifentanil from 0.055 to 5.5 μg·kg⁻¹·min⁻¹. A second group received constant rate infusions of remifentanil of 1.0 μg·kg⁻¹·min⁻¹ for 6–8 h. Enflurane MAC was measured before, hourly during remifentanil infusion, and at the end of the experiment after naloxone administration. A third group received alternating infusions of 0.5 and 1.0 μg·kg⁻¹·min⁻¹ with MAC determinations made 30 min after each change in the infusion rate. Heart rate, mean arterial pressure, and remifentanil blood concentrations were measured during MAC determinations.

Results: Enflurane MAC was reduced up to a maximum of 63.0 ± 10.4% (mean ± SD) in a dose-dependent manner by remifentanil infusion. The dose producing a 50% reduction in the enflurane MAC was calculated as 0.72 μg·kg⁻¹·min⁻¹ and the corresponding blood concentration was calculated as 9.2 ng/ml. Enflurane MAC reduction remained stable during continuous, constant rate infusions for periods of 6–8 h without any signs of tolerance. Recovery of enflurane MAC to baseline occurred in 30 min (earliest measurement) after stopping the remifentanil infusion.

Conclusions: Remifentanil is equally efficacious and about half as potent as fentanyl, judging from the blood concentra-
tions causing equivalent reductions in enflurane MAC in the dog. The characteristics of MAC reduction are similar to those of other opioids, including the ceiling effect. Recovery from remifentanil anesthesia is much more rapid than for any other opioid studied to date, especially after continuous infusions maintained for 6 or more h. (Key words: Anesthetics, intravenous: remifentanil. Anesthetics, volatile: enflurane. Antagonists: naloxone. Opioids: remifentanil. Potency: minimum alveolar concentration.)

The use of opioids in anesthetic practice is predicated on their ability to block sympathetic (hypertension, tachycardia) and somatic (coughing, movement) responses to noxious stimulation. Administration of an opioid to a target range of plasma concentrations can block responsiveness to noxious stimuli for many patients. However, the use of opioids alone to prevent responses to noxious stimulation requires the administration of large doses for a prolonged time in some patients, resulting in accumulation of opioid and prolonged recovery from its effects, especially respiratory depression.

Remifentanil, the hydrochloride salt of 3-[4 -(methoxy-carbonyl)-4-(1-oxopropyl) phenylamino]-1-piperidine] propanoic acid methyl ester, formerly designated as G18708A, is a new synthetic opioid exhibiting μ-opioid receptor-mediated effects, analogous to those of structurally related phenylpiperidine derivatives such as fentanyl and sufentanil. The unique characteristic of remifentanil is the propanoic acid methyl ester linkage on the piperidine nitrogen, which renders it susceptible to metabolism by nonspecific esterases in blood and tissues. The terminal half-life of remifentanil in humans ranges from 10 to 21 min, and a computer simulation showed that its context-sensitive half-time is less than 5 min no matter how large the dose or how long the infusion. Remifentanil is distinguished from the rest of the phenylpiperidine opioids by not only having a rapid onset and a short latency to its peak effect but also a rapid recovery. With these characteristics, remifentanil should facilitate administration by either variable-rate infusion titrated to individual patient needs or a constant-rate infusion targeted at the
EC₉₀ (the drug concentration that will produce a given effect in 99% of the subjects) for suppression of responses to all intensities of noxious stimulation. The minimum alveolar concentration (MAC) at which an inhaled anesthetic agent suppresses the response to a standard stimulus in 50% of the subjects is used as a measure of anesthetic potency. The ability of opioids to reduce the MAC of enflurane in dogs facilitates comparisons of opioids and other drugs in terms of their anesthetic potency and efficacy.²⁻⁷ For drugs with contrasting pharmacokinetic profiles (e.g., fentanyl vs. remifentanil), a comparison can be established by maintaining stable plasma concentrations. Responses to tail-clamping in dogs seems also to allow extrapolation to the equivalent stimulus of skin incision in humans.⁸

Materials and Methods

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

Mongrel dogs (N = 25) weighing 33.9 ± 3.3 kg (SD) were given an intravenous dose of 0.1 mg/kg succinylcholine mixed with 0.015 mg/kg glycopyrrolate, and anesthesia was simultaneously induced with 5% enflurane in oxygen using a specialized mask and a Bain anesthesia circuit. Succinylcholine permitted immediate administration of a high concentration of enflurane and facilitated a rapid induction without the potential discomfort that the animal may experience while struggling during a slower induction.⁹ Auffed tube was placed in the trachea and mechanical ventilation was controlled by a Harvard respirator (South Natick, MA), adjusted to maintain normocarbia as determined by arterial blood gases. Lactated Ringer's solution was infused through a foreleg intravenous cannula at a rate of 4 ml·kg⁻¹·h⁻¹. An esophageal probe allowed monitoring of body temperature, which was maintained through the use of a warming blanket within 1°C of the temperature measured after induction of anesthesia. The electrocardiogram was monitored continuously. A percutaneous femoral artery catheter was used for continuous blood pressure monitoring on a strip chart recorder and for periodic sampling of arterial blood for gas analysis and determination of whole blood concentrations of remifentanil and its principal metabolite (GR90291). The blood volume removed was replaced by an equal volume of 5% albumin injected intravenously after each sample.

Assessment of Anesthesia

End-tidal enflurane concentration was measured with a Beckman LB-2 (Fullerton, CA) infrared analyzer calibrated before each experiment. The tail clamp method was used to determine enflurane MAC.³ Expired enflurane was adjusted in 0.2% increments or decrements. Minimum alveolar concentration was defined as the end-tidal concentration midway between the end-tidal concentrations of enflurane at which the animal did and did not move in response to the applied stimulus.

To determine the concentrations of remifentanil and its main metabolite in whole blood, 1-ml aliquots of arterial blood were immediately placed in two volumes of acetonitrile (first 11 animals) or 50% citric acid solution (last 14 animals) to arrest esterase activity followed by four volumes of methylene chloride to extract remifentanil and the metabolite into the organic phase. The samples were then stored at −70°C until the time of analysis. Blood concentrations of remifentanil were determined by gas chromatography with high-resolution mass spectrometry and selective ion monitoring (GC-HRMS-SIM)¹⁰ and duplicate samples were analyzed by high-pressure liquid chromatography (see Appendix) and verified by the manufacturer (Glaxo Research Triangle Park, NC).

Experimental Protocol

After waiting at least 1 h after the induction of enflurane anesthesia, control enflurane MAC was determined. In the first set of experiments, six dogs received incremental infusions of remifentanil (Glaxo) at rates from 0.055 to 5.5 µg·kg⁻¹·min⁻¹. When each infusion rate had been constant for 30 min, enflurane MAC was determined and an arterial blood sample was obtained for remifentanil assay. After the entire infusion sequence was completed, the infusion rate was decreased to that previously causing a 30–40% decrease of enflurane MAC, and MAC was again determined at that infusion rate. Finally, the remifentanil infusion was stopped and the last measurement of MAC was obtained 30 min later.

In the second set of experiments, the stability of remifentanil blood concentrations and the MAC-reducing effect were evaluated during a prolonged constant rate infusion of 0.6 µg·kg⁻¹·min⁻¹ in five dogs, and 1.0 µg·kg⁻¹·min⁻¹ in eight dogs. Remifentanil concentrations and enflurane MAC were determined before and every hour after starting the infusion.

ANESTHETIC POTENTIALS

In the third set of experiments, 1.0 µg·kg⁻¹·min⁻¹ of remifentanil was infused to determine the MAC for each infusion rate. Remifentanil MAC were determined at each infusion rate.

At the end of each experiment, the sequence was repeated, and each dog was reanesthetized with enflurane MAC was determined.

Data Analysis and Statistical Considerations

Remifentanil infusions were compared versus enflurane MAC by linear E₉₀ regressions, where E = % remifentanil blood concentrations, and MAC = enflurane MAC determined by 50% and γ = 1.0. The slope of the dose-response curve and the dose-responsive regression was used to compare remifentanil infusions.

Analysis of variance was used to compare mean values at the three time points, and P < 0.05 was considered significant. Values are presented as means ± SD.

Results

Incremental changes in remifentanil produced proportional changes in MAC. Before remifentanil MAC was determined, 5.0 ± 10.4 µg·kg⁻¹·min⁻¹ of remifentanil produced an increase in MAC of 63.0 ± 10.4%, and 0.6 µg·kg⁻¹·min⁻¹ of remifentanil was not significantly different from the corresponding control MAC in the linear E₉₀ model.

Anesthesiology. V 84, No 4, Apr 1996
In the third set of experiments, infusions of 0.5 and 1.0 µg·kg⁻¹·min⁻¹ were alternated repeatedly in six dogs to determine the consistency of the MAC reduction with each infusion rate and blood concentration over time. Remifentanil concentration and enflurane MAC were determined at least 1 h after each change in the infusion rate.

At the end of either a continuous infusion or an alternating sequence of infusion rates, 0.1 mg/kg naloxone was given, enflurane MAC determined and compared to the control MAC in 13 of the dogs. In six dogs, the remifentanil infusion was stopped, and 30 min later MAC was determined and compared to control MAC.

**Data Analysis and Statistics**

Remifentanil infusion rates and blood concentrations versus enflurane MAC reductions were fitted to a non-linear $E_{\text{max}}$ regression model:\[ E = \frac{E_{\text{max}} \cdot C}{EC_{50} + C} \]

where $E = \%$ reduction of enflurane MAC, $C =$ remifentanil blood concentration, $E_{\text{max}} =$ maximum obtainable enflurane MAC reduction, and $EC_{50} =$ remifentanil blood concentration when enflurane MAC was reduced by 50% and $\gamma =$ dimensionless exponent that determines the slope of the concentration-effect curve. In the dose-response analysis, concentrations of remifentanil were replaced by the infusion/infusion dose. Linear regression was used to assess the correlations between remifentanil infusion rate and its blood concentrations. Analysis of variance followed by Scheffe’s F test was used to compare values at the different measurement points, and $P < 0.05$ was considered statistically significant. Values are expressed as mean ± SD.

**Results**

Incremental changes in the remifentanil infusion rate produced proportional increases in remifentanil concentrations in blood (fig. 1). Control enflurane MAC before remifentanil administration was 2.1 ± 0.2%. Enflurane MAC was reduced by all remifentanil doses, with a 63.0 ± 10.4% reduction at the infusion rate of 1.0 µg·kg⁻¹·min⁻¹. Higher infusion rates produced only small additional decreases in MAC that were not statistically significant. When infusion rates were related to the corresponding enflurane MAC reductions in a non-linear $E_{\text{max}}$ model, a maximum reduction of 71.4% was predicted (fig. 2). The dose producing a 50% reduction in the enflurane MAC solved from the same regression equation was 0.715 µg·kg⁻¹·min⁻¹ (95% confidence limits 0.687–0.745 µg·kg⁻¹·min⁻¹). A ceiling to the enflurane MAC reduction also was apparent when blood concentrations were at and greater than 10–15 ng/ml (fig. 3). The concentration versus response curve describing the $E_{\text{max}}$ model predicted a maximum MAC reduction of 75.1%. The $EC_{50}$ was 9.2 ng/ml (95% confidence limits 8.59–10.01 ng/ml). The MAC measured at the end of the experiments after stopping remifentanil infusion with and without injection of naloxone was 2.1 ± 0.19%, which was not different from the control enflurane MAC.

The main hemodynamic change produced by remifentanil was a dose-dependent decrease in heart rate, which was reduced by approximately 35% compared to the baseline heart rate with enflurane alone. Near maximal decreases occurred at infusion rates of 0.6 µg·kg⁻¹·min⁻¹ or less (fig. 4). The mean arterial pressure did not vary significantly with remifentanil, although there was a tendency toward higher systolic and lower diastolic arterial pressures along with the
slower heart rate. Naloxone completely antagonized the heart rate reductions caused by remifentanil.

Prolonged infusions of remifentanil produced a persistent reduction of enflurane MAC with no trend or significant change in the degree of MAC reduction over time (fig. 5). There was a statistically significant difference between the MAC reduction produced by an infusion of 0.5 $\mu$g·kg$^{-1}$·min$^{-1}$ and that of 1.0 $\mu$g·kg$^{-1}$·min$^{-1}$ of remifentanil, and this difference was maintained over time even when the infusion rates were alternated (fig. 6).

Analysis of the principal metabolite of remifentanil (GR90291) in the dogs receiving prolonged infusions showed that its concentration increased over time reaching a plateau 4 or 5 h after starting the infusion of remifentanil. The peak concentrations measured were 77.0 ± 4.4 ng/ml (fig. 7). The concentration of GR90291 started to decline at 450–500 min, the period when remifentanil was decreased to 0.5 $\mu$g·kg$^{-1}$·min$^{-1}$, and continued to decrease slowly after discontinuation of remifentanil.

Discussion

The ability to reduce the MAC of volatile anesthetics is a measure of the anesthetic activity of all central nervous system depressants, and it allows comparisons of both potency (dose or concentration for a given MAC reduction) and efficacy (maximum obtainable MAC reduction). In the standard dog model of MAC reduction, we found that remifentanil had significant anesthetic activity. Table 1 compares the enflurane MAC reduction produced by different opioids in the same dog model.12357 Like other opioids, the maximum MAC reduction approximated 70%, which was unchanged by two or three times larger doses (ceiling effect). Although the extremely rapid clearance of remifentanil allows a rapid recovery even after large doses are given, it is unlikely that this drug alone could be used as a complete anesthetic because the limiting factor will be the maximum intrinsic activity inherent in all $\mu$-type opioids.

Fig. 2. Remifentanil dose versus effect. Infusion rate in micrograms per kilogram per minute versus percent reduction of enflurane minimum alveolar concentration relationship as analyzed by nonlinear regression. ED$$_{50}$ is the dose causing 50% reduction of enflurane minimum alveolar concentration.

Fig. 3. Remifentanil concentration versus effect (blood concentration in nanograms per milliliter versus percent reduction of enflurane minimum alveolar concentration) relationship as analyzed by nonlinear regression. EC$$_{50}$ is the concentration causing 50% reduction of enflurane minimum alveolar concentration.
ANESTHETIC POTENCY OF REMIFENTANIL IN DOGS

The main remifentanil metabolite is the decarboxylated carboxylic acid (GR90291). It is a pure \( \mu \)-agonist with a potency 1/2000 to 1/4000 that of remifentanil.\(^{13-15}\) Pharmacokinetic analysis in humans shows that this metabolite has a terminal half-life six or seven times longer and a steady-state concentration 12 times higher than that of remifentanil.\(^4\) In theory, if enough metabolite accumulates it could bind to the \( \mu \)-receptors, producing a long-lived duration of effect. That the effect of remifentanil did not change during prolonged infusions and that the MAC reduction seen paralleled the concentration of remifentanil and not that of GR90291 suggests that the metabolite does not alter the effect of remifentanil administered in this dose range and over a 6–8-h duration of the infusion. The concentrations of metabolite measured during the study did not exceed 80 ng/ml whereas simultaneous remifentanil concentrations were 9–12 ng/ml. Because the metabolite is such a weak agonist, these concentrations are too low to provide any significant additive effect to the action of remifentanil.

Titration of remifentanil to effect is facilitated by a rapid blood-brain equilibration.\(^6\) Rapid clearance from effect sites (context sensitive half-time = 3.7 min) even

---

Fig. 4. Heart rate and reduction of enflurane minimum alveolar concentration as functions of remifentanil dose rate in micrograms per kilogram per minute. Each line represents data for an individual animal (n = 6, the first set of experiments).

Fig. 5. Enflurane minimum alveolar concentration reduction with remifentanil over time; effect of 1.0 \( \mu \)g kg\(^{-1}\) min\(^{-1}\) (n = 8). Error bars represent ± the SD.

---

The use of opioids in anesthetic practice is predicated on their ability to block sympathetic (hypertension, tachycardia) and somatic (coughing, movement) responses to noxious stimulation. For a number of reasons (variability in dosage requirements among patients and within an individual patient; variable intensities of stimulation; lack of a graded method to monitor opioid effect, especially in a paralyzed patient; greater difficulty in reversing a response to stress than in preventing it; and absence of dose-related side effects and toxicity in a tracheally intubated patient whose lungs are mechanically ventilated), the anesthesiologist finds it more reliable and convenient to employ opioids in large doses as primary anesthetic agents and to maintain opioid concentrations at the upper levels of their therapeutic ranges. The larger the dose and the longer the maintenance of high concentrations of presently available opioids, the greater their accumulation in the body and the longer the time required for recovery from their effects, especially ventilatory depression. Precise titration of opioid administration according to the individual patient’s needs is difficult for the reasons cited earlier and often is impractical because of the pharmacokinetic clearance currently available. An alternative because to increase or suppress the majority of the patient’s response to the infusion of remifentanil.

The steady-state concentration is essentially compared to the anesthetic MAC, tail clamping, or the equivalent to surmount the MAC values. This is the basis for comparisons and also suggests that remifentanil is more potent than fentanyl. Remifentanil has a longer duration of action than fentanyl because of its plasma, and the anesthetic concentration may become more potent than is intended. The increase in the concentration of remifentanil is time and dose dependent. A 1:1 increase in the concentration of remifentanil at 5 min appears to be about the same as the effect of fentanyl.

Fig. 7. Concentration in nanograms per milliliter of blood of the main metabolite of remifentanil (GR90291) over time (in min) in dogs receiving prolonged infusions of remifentanil (4–6). The dotted area represents the period where the remifentanil infusion was decreased by 50%. After measuring minimum alveolar concentration at this level, the remifentanil infusion was stopped.

**Table 1. Enflurane Minimum Alveolar Concentrations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enflurane Minimum Alveolar Concentrations (MAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.96</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>0.75</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.85</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Note: MAC = not applicable.

* Whole blood.

---

Anesthesiology, V 84, No 4, Apr 1996
ANESTHETIC POTENCY OF REMIFENTANIL IN DOGS

Table 1. Enflurane Minimum Alveolar Concentration Reduction in Dogs with Different Opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum % Enflurane MAC Reduction</th>
<th>Largest Dose</th>
<th>Highest Plasma Concentration (ng/ml)</th>
<th>EC50 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>67 ± 3</td>
<td>27 ng/kg</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>70 ± 2</td>
<td>720 µg/kg + 80 µg·kg⁻¹·min⁻¹</td>
<td>2,613 ± 247</td>
<td>54</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>68 ± 2</td>
<td>5.5 µg·kg⁻¹·min⁻¹</td>
<td>103 ± 10.6*</td>
<td>9.2*</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>66 ± 2</td>
<td>270 µg/kg + 3.2 µg·kg⁻¹·min⁻¹</td>
<td>97 ± 31.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>78 ± 2</td>
<td>501 µg/kg</td>
<td>51 ± 4.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

NA = not applicable

* Whole blood.

The steady-state plasma concentrations required to suppress the response to a given stimulus are used to compared the anesthetic potency of drugs. In terms of MAC, tail clamping in dogs is believed to be a stimulus equivalent to surgical skin incision in humans. Enflurane MAC reduction by different opioids provides a basis for comparison of their potency, and this datum also suggests that the anesthetic potencies of opioids in humans and dogs are similar. Because of the way remifentanil is metabolized, the concentration of remifentanil has to be measured in whole blood instead of plasma, and the distribution of remifentanil between blood cells and plasma is not known. The blood concentration of remifentanil causing 50% enflurane MAC reduction (EC50) was 9.2 ng/ml, whereas this same effect is produced by a fentanyl plasma concentration of 5.5 ng/ml in the dog. Using the established partition coefficient of fentanyl and mean hematocrit value for dogs (0.49 ± 0.05), a plasma fentanyl concentration of 5.5 ng/ml would correspond to a whole blood concentration of 5.16 ng/ml. On this basis, remifentanil appears to be about one half as potent as fentanyl. Applying the same logic to alfentanil (EC50 = 54 ng/ml of plasma or 33.6 ng/ml of whole blood), the corresponding blood concentration ratio between alfentanil and remifentanil should be 3.6:1. So far, there are limited studies to compare these results. Studies showing a remifentanil EC50 of 14.7–19.5 ng/ml for shifting of the spectral edge in human volunteers are in accordance with our results. However, a potency ratio of 3.2:1 between alfentanil and remifentanil blood concentrations was found in a study achieving equivalent depression of the respiratory minute-volume. Clearly, valid comparisons of the relative potencies of opioids mandate the use of similar endpoints or stimuli against which those comparisons are made.

Remifentanil, like other opioids, caused a dose-dependent reduction of the heart rate. Most of this effect was evident at small doses and the dose-response curve for heart rate reduction had a steeper slope and peaked at a lower concentration than the anesthetic-sparing effect. A decrease in heart rate was typically observed when remifentanil was administered with isoflurane for induction of anesthesia in humans. No consistent changes in blood pressure were observed in this study in which the measurements were always made at equivalent (1 MAC) levels of anesthesia.

In conclusion, the potency of remifentanil is about one half that of fentanyl, judging by the blood concentrations producing equivalent decreases in the enflurane MAC in dogs. Remifentanil is no more efficacious than other opioids of the piperidine family, with a ceiling effect close to 70%. Its effect over time is sustained and recovery is rapid even after prolonged infusion.

References


Appendix

Blood samples (5 ml) were collected in heparinized Vacutainer tubes (Becton-Dickinson, Rutherford, NJ). A 1 ml aliquot was pipetted into a glass tube containing 20 μl of 50% citric acid and vortexed to ensure mixing. Samples were kept frozen at −70°C until analysis (1–8 weeks). At the time of analysis, 2 ml acetonitrile and 50 ng fentanyl (as an internal standard) were added to each sample. After vortexing, 5 ml methylene chloride was added. Samples were mixed by vortexing, and centrifuged for 5 min at 1000g to aid in clear separation of the layers. The lower organic layer was removed and applied to a Extrelut QE column (EM Separation, Gießen, NJ). After 5 min equilibration, remifentanil and fentanyl were eluted with additional 5 ml methylene chloride. Organic solvent was evaporated to dryness at 45°C under a gentle stream of nitrogen. The samples were reconstituted with 40–60 μl toluene, transferred to gas chromatography vials, which were loaded onto an autosampler, and 1 μl aliquots were injected into an HP5890GC (Hewlett-Packard, Palo Alto, CA) equipped with a nitrogen-phosphorus detector operated at 250°C. Injector temperature was maintained at 250°C. Separation was accomplished using fused silica megabore silicone (HP-1) column (10 m x 0.53 mm ID, 2.65 μm film thickness, Hewlett-Packard). Oven temperature was kept isothermal at 255°C for 14 min and then ramped to 270°C at 8°C per min. The carrier and makeup gas for the detector was ultrapure grade helium at a flow of 6.5 ml/min, and 30 ml/min, respectively. Under these chromatographic conditions, remifentanil eluted at ~7.2 min and the internal standard (fentanyl) at ~11.2 min.

Standards and quality control samples were processed in the same fashion as described earlier using drug free whole blood spiked with known concentrations of remifentanil (0–100 ng/ml). The concentrations of remifentanil in blood samples were calculated using the regression parameters obtained from the calibration curve. The lower limit of detection was 4.0 ng/ml and the coefficient of variation was 11.0% at 5 ng/ml, 6.8% at 50 ng/ml, and 5.0% at 100 ng/ml.

Background: α2-Adrenergic agonists such as dexmedetomidine are used for sedation in humans. The possibility of a REM-like state as a mechanism to explain the sleep-like state occurring in patients receiving dexmedetomidine was first suggested in 2007. However, no studies have been performed to investigate the REM-like state specifically in dexmedetomidine sedation. We performed a prospective, randomized, controlled study to evaluate the REM-like state and sleep architecture in patients sedated with dexmedetomidine.

Methods: After obtaining institutional review board approval, we recruited patients with a body mass index (BMI) between 18 and 35. We excluded patients with a sleep disorder, a history of drug addiction or alcoholism, a history of sleep disorders, and those who were pregnant or lactating. The patients were divided into the following two groups: the dexmedetomidine group and the control group. In the dexmedetomidine group, dexmedetomidine was infused at a dose of 0.5 µg/kg/hour for 90 minutes. In the control group, we administered saline as a placebo. We performed multichannel overnight polysomnography in all patients. The sleep architecture was evaluated using the American Academy of Sleep Medicine scoring manual.

Results: The patients were divided into the following two groups: the dexmedetomidine group and the control group. In the dexmedetomidine group, the sleep architecture was similar to that of normal sleep, with a decrease in rapid eye movement (REM) sleep duration and an increase in non-REM (NREM) sleep. In the control group, the sleep architecture was similar to that of normal sleep.

Conclusions: Our results suggest that dexmedetomidine sedation induces a sleep-like state similar to that of normal sleep, with a decrease in REM sleep duration and an increase in NREM sleep. Therefore, dexmedetomidine sedation may be a safe and effective treatment for patients with sleep disorders.