Dose Comparison of Remifentanil and Alfentanil for Loss of Consciousness


Background: This study evaluated the efficacy and safety of remifentanil, a potent mu agonist opioid with a rapid onset and offset of effect, as a sole induction agent for loss of consciousness (LOC) and compared it with alfentanil.

Methods: Remifentanil and alfentanil were administered intravenously over 2 min in ascending doses (remifentanil 2, 3, 4, 5, 6, 8, 10, 15, 20 μg/kg; alfentanil 40, 60, 80, 100, 120, 160, 200 μg/kg) to unpremedicated healthy patients. Patients were observed for rigidity and LOC for 30 s after the end of infusion. If patients had not lost consciousness, 2 mg·kg⁻¹·min⁻¹ thioental was administered until LOC was achieved. Arterial blood samples, obtained at specified time intervals, were analyzed for remifentanil and alfentanil whole-blood concentration. Blood pressure and heart rate were also recorded at preset time intervals.

Results: Neither drug could reliably produce LOC with both drugs, there was a dose-dependent decrease in thioental requirements and a dose-dependent increase in the incidence and severity of rigidity (P < 0.05). The median effective dose (ED₅₀) for LOC with remifentanil was 12 μg/kg, and for alfenta

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REMIFENTANIL is a new ultra-short-acting opioid that is 20–50 times more potent than alfentanil in its analgesic and respiratory depressant effects.1 Chemically, it is a hydrochloride salt of 3-[4-methoxy carbonyl-4-[1-oxopropyl]phenylamino]-1-piperidine propionic acid, methyl ester.2 This compound is unique among opioids in that the ester bond makes it susceptible to hydrolysis by esterases in plasma and other tissues.

The pharmacokinetics of remifentanil have been described previously.1,3,4 Remifentanil has a small volume of distribution, a rapid distribution phase, and a short elimination half-life.1,3,4 The onset of effect of remifentanil is rapid with a rate constant for equilibration between plasma and effect compartment similar to alfentanil.5 At equipotent analgesic bolus doses (given over 1 min), alfentanil and remifentanil have a similar onset and duration of analgesic and respiratory depressant effects.1 In addition, the context-sensitive half-time for remifentanil is considerably less than that for alfentanil (3.65 min compared with 58.5 min after a 4-h infusion) and does not increase with prolonged administration.5 These properties produce an extremely rapid termination of action.

In previous studies, alfentanil provided rapid induction, caused minimal cardiovascular alterations, and effectively blunted hemodynamic responses to laryngoscopy and intubation.5,6 However, when administered in a relative large dose as an induction agent, the possibility of residual effects of alfentanil at the end of surgery...
remains a major deterrent to its use in this way. The rapid termination of effect of remifentanil may make it more suitable for use as an induction agent. Therefore we designed our study to evaluate the efficacy and safety of remifentanil for anesthetic induction and to compare it with alfentanil.

Methods

The study was approved by the Institutional Review Board for Human Investigation at Duke University Medical Center, and written informed consent was obtained from patients before they were enrolled. Nonpregnant patients between the ages of 18–65 yr who weighed less than 100 kg and were within 35% of ideal body weight with American Society of Anesthesiologist physical status 1 or 2 and scheduled for elective surgery were recruited for the study. No patient was enrolled more than once. Patients with known idiosyncrasies or allergy to opiates, with a history of alcohol or drug abuse or a major psychiatric illness were excluded. Other exclusion criteria consisted of neurosurgical, cardiothoracic or major vascular procedures, smoking > 20 cigarettes per day, or anesthesia or use of opiates during the previous week.

Seven ascending doses of either remifentanil (2, 3, 4, 5, 6, 8, 10, 10 μg/kg) or alfentanil (40, 60, 80, 100, 120, 160, 200 μg/kg) were administered. Ten patients were included in each dose group and randomly assigned to receive either remifentanil or alfentanil (n = 5 in each drug group). Both the patient and the investigators were unaware of the opiate administered. Once recruitment to these dosage groups was completed, an additional 15 patients were enrolled to define more adequately the maximum responses to remifentanil and alfentanil. They were randomized to receive 15 or 20 μg/kg remifentanil and 200 μg/kg alfentanil (n = 5 per group).

Safety data at each dose tier were evaluated before the next dosing level was begun.

A radial arterial cannula was inserted on the day of surgery for continuous measurement of blood pressure and for intermittent blood sampling for subsequent measurement of whole-blood concentrations of the study drugs. A peripheral venous cannula was also inserted in the contralateral arm for infusion of remifentanil or alfentanil. A standard lead II electrocardiogram was continuously monitored.

Patients did not receive any premedication. Oxygen (100%) was administered for at least 3 min before induction. D-tubocurarine (3 mg) was administered approximately 2 min before infusion of the study drug. All doses of remifentanil and alfentanil were prepared to an equal volume, which was administered as a constant rate infusion during a 2-min period. After initiation of the infusion, the patients were asked to open their eyes and take a deep breath every 10 s. Failure to respond to three consecutive commands was considered loss of consciousness (LOC) and the time of LOC was noted. If the patient did not lose consciousness within 30 s after the end of study drug infusion, thiopental was infused at a rate of 2 mg·kg⁻¹·min⁻¹ via a syringe pump (Ohmeda 9000, Stenton, West Yorkshire, UK) until the patient became unconscious.

Succinylcholine (1.5 mg/kg) was administered intravenously after LOC. Tracheal intubation was performed 1 min after the succinylcholine was administered. Anesthesia was maintained with 66% nitrous oxide in oxygen. Isoflurane was administered when a hemodynamic response indicated inadequate anesthesia. Opiates (other than remifentanil or alfentanil) were administered only after 60 min had elapsed, by which time blood samples for pharmacokinetic analysis had been obtained.

Blood pressure and heart rate were recorded before operation; before administration of d-tubocurarine; before the start of the infusion of the study drug; 1 min after the start of the infusion; at the end of the infusion; before tracheal intubation; and 1, 3, and 5 min after tracheal intubation. Baseline blood pressure was determined as the mean of the two lowest values of systolic blood pressure (SBP) recorded on the evening before surgery, on the morning of surgery, and immediately before administration of d-tubocurarine. Ephedrine (5–10 mg) was administered if the SBP decreased by 30 mmHg or more from the baseline value. Atropine (0.5 mg) was administered intravenously if the heart rate decreased to less than 40 beats/min.

Rigidity of the chest wall, abdominal wall, and extremity muscles was assessed 1 min after the start of the infusion, at the end of the infusion, and before succinylcholine administration. Muscle rigidity was graded on a four-point scale with 0 = no rigidity, 1 = mild, 2 = moderate, and 3 = severe rigidity. In addition, pain at the infusion site during the infusion of the study drug or any electrocardiographic abnormality occurring during the course of the surgical procedure were recorded. Patients were asked the day after their surgery if they had recall of any aspect of their operation.

Arterial blood samples were collected to measure whole-blood concentrations of either remifentanil or
alfentanil before their administration; 30 s after the end of infusion; immediately before intubation; 3, 5, 10, 20, 30, 45, and 60 min after tracheal intubation; and at the time of skin incision. The concentrations were determined by gas chromatography high-resolution mass spectrometry with selected ion monitoring.\textsuperscript{7,8} The validated concentration range for remifentanil was 0.1 - 5 ng/ml. Samples with concentrations outside this range were reassayed using an improved procedure with a range of 0.1 - 250 ng/ml. The validated range for the alfentanil whole-blood assay was 1 - 3,000 ng/ml.

Statistical Analysis

Thiopental requirements after either remifentanil or alfentanil administration were compared by analysis of variance, and hemodynamic values at each of the stated time points were compared within groups using paired \( t \) tests and between groups by repeated-measures analysis of variance. Further analyses of hemodynamic values were performed among patients who did not receive thiopental to examine changes from baseline to preintubation values and from preintubation to postintubation values. Changes were assessed by \( t \) test and then by linear regression controlling for baseline values. Logistic regression analysis was performed to describe a log-dose-response relation and to determine the median effective dose (ED\(_{50}\)) for LOC and its 95% confidence intervals (CI) for the remifentanil and alfentanil treatment groups. The significance of the covariates age, weight, sex, ethnic origin, and ASA physical status on this relation was also determined. Logistic regression was performed on the highest measured remifentanil and alfentanil blood concentrations.

Results

The protocol was designed to include 45 patients in 9 dose tiers in the remifentanil group (5 patients in each of 2, 3, 4, 5, 6, 8, 10, 15, and 20 \( \mu \)g/kg dose tiers) and 40 patients in 7 dose tiers in the alfentanil group (5 patients in each of 40, 60, 80, 100, 120, and 160 \( \mu \)g/kg dose tiers and 10 patients in the 200 \( \mu \)g/kg dose tier). However, one patient received 200 \( \mu \)g/kg alfentanil instead of 15 \( \mu \)g/kg remifentanil, and thus an additional patient was recruited in the remifentanil group. One patient in the remifentanil group received only one half of the study drug and was replaced. One patient in the alfentanil group received the study drug over a period of 4 min instead of 2 min. This patient was also replaced. Thus 88 patients, of whom 46 received remifentanil and 42 received alfentanil, were studied. In the remifentanil group, the mean age and weight were 47 ± 13 yr and 76.6 ± 13.8 kg, respectively. In the alfentanil group, the mean age and weight were 43 ± 14 yr and 74.8 ± 12.7 kg, respectively (\( P > 0.05 \)).

Loss of Consciousness

The development of severe rigidity at larger doses of the study drugs made it difficult in some patients to differentiate between movement due to rigidity and LOC after the end of infusion, and as a result, these patients in the larger dose groups were observed for a further 10 s to assure the observer of LOC before succinylcholine was administered. The percentage of patients losing consciousness with the two opioids in each dose group without the need for thiopental administration is presented in Figure 1. Doses of remifentanil ≤ 5 \( \mu \)g/kg (i.e., 2, 3, 4, or 5 \( \mu \)g/kg) or alfentanil ≤ 80 \( \mu \)g/kg (i.e., 40, 60, or 80 \( \mu \)g/kg) were ineffective in all patients in producing LOC. Thus all 35 patients in these subgroups required thiopental to induce LOC. More than 70% of patients who received 10 \( \mu \)g/kg or more of remifentanil lost consciousness. Fewer than 50% of patients in the alfentanil group who received doses > 80 \( \mu \)g/kg lost consciousness. The ED\(_{50}\) for LOC with these two opioids can be estimated from these curves to be 12 \( \mu \)g/kg (95% CI, 9 - 19 \( \mu \)g/kg) for remifentanil and 176 \( \mu \)g/kg (95% CI, 126 - 653 \( \mu \)g/kg) for alfentanil.
Analysis of the data revealed an age-related effect for LOC with remifentanil (P = 0.02) but not with alfentanil (P = 0.9). Older patients in this study required lower doses of remifentanil for LOC.

To describe the relation between the effect and concentration of these opioids, the median effective concentration (\(EC_{50}\)) for LOC was determined from the highest measured whole-blood concentrations. Four patients receiving remifentanil and six patients receiving alfentanil were excluded from this analysis because the blood samples at 30 s after infusion were missed. Both highest measured drug concentration (P = 0.04) and age (P = 0.045) were significant variables within the model for remifentanil, whereas only highest measured drug concentration (P = 0.03) was significant for alfentanil. The \(EC_{50}\) was estimated to be 53.8 ng/ml (95% CI, 33.7 - 102.3 ng/ml) for remifentanil (fig. 2) and 1,012 ng/ml (95% CI, 711 - 9,49 ng/ml) for alfentanil (fig. 3). Thus the effect-concentration relation shows a potency ratio of approximately 19 between remifentanil and alfentanil.

**Thiopental Use**

One patient in the 6 \(\mu g/\text{kg}\) remifentanil dose tier received only 50% of the study drug, and the time of LOC was not recorded. Thus this patient was excluded from the calculation of thiopental use. Figure 4 shows the mean dose of thiopental required to obtain LOC at each dose level for both drugs. There was an overall reduction in thiopental requirements as the dose of alfentanil and remifentanil increased. Doses of thiopental within the same dose tier were generally lower in the alfentanil group than in the remifentanil group.

**Hemodynamic Effects**

The mean baseline values for SBP and diastolic blood pressure and heart rate were similar for each dose tier and treatment group. The within-treatment tests showed no statistically significant changes in SBP or heart rate from the baseline values to just before intubation with either remifentanil or alfentanil (P > 0.05). The changes in diastolic blood pressure from the baseline to preintubation, although significant for both remifentanil (P = 0.0001) and alfentanil (P < 0.01), were
not considered clinically significant. No patient had a decrease in SBP of 30 mmHg or more, and thus no patient required ephedrine.

When data from all the dose groups were pooled, a significant treatment difference in the maximum changes in SBP and heart rate within 5 min after intubation (P < 0.05 and 0.001, respectively) was found. The changes were dose independent, with patients receiving remifentanil displaying greater increases in SBP (44 ± 26 mmHg) and heart rate (19 ± 17 beats/min) than did those receiving alfentanil. The patients receiving remifentanil also had greater increases in diastolic blood pressure (21 ± 18 mmHg) than did those receiving alfentanil (14 ± 15). Overall, the increase in SBP and heart rate after intubation were greater after remifentanil than after alfentanil (P < 0.05 and P < 0.001, respectively).

Twelve patients in the remifentanil group and eight patients in the alfentanil group did not require thiopental. Among these patients, no significant differences were found between treatments in the changes from baseline to preintubation. However, for SBP and heart rate, the change from pre- to postintubation values was significantly greater in the remifentanil group (P = 0.01 and P = 0.0001, respectively, by t test). Similar results were found after controlling for baseline values. Dose level was also a significant determinant of the change in SBP and heart rate from pre- to postintubation time (P = 0.01 and P = 0.003, respectively), with increasing dose having a decreasing effect.

The whole-blood concentrations of remifentanil measured before intubation had decreased by an average of 71% from its highest measured postinfusion value compared with only a 47% decrease for alfentanil (P < 0.0001).

Adverse Events

There was a dose-related increase in the incidence and the severity of muscle rigidity after administration of both remifentanil and alfentanil. The proportion of patients developing rigidity and the severity of rigidity just before succinylcholine administration are shown in figure 5. Rigidity developed in more than 80% of patients who received remifentanil at doses ≥ 8 µg/kg, and severe rigidity developed in 60% of patients who received 20 µg/kg remifentanil. Muscle rigidity developed in all patients who received 120 µg/kg or more of alfentanil. None of the patients who were given less than 4 µg/kg remifentanil or less than 80 µg/kg alfentanil developed severe muscle rigidity. The relation between log-dose of remifentanil or alfentanil and maximum severity of muscle rigidity was significant in the remifentanil (P < 0.05) and in the alfentanil (P < 0.001) group.

One patient who received 60 µg/kg alfentanil reported venous irritation. No other patient in either group displayed any sign of venous irritation or thrombophlebitis.

No patient reported recall of any aspect of the operation in either the remifentanil or alfentanil groups.

Discussion

Previous reports have shown that remifentanil has rapid onset and offset of effect. 1, 3 In addition, it is noncumulative when administered over a prolonged period because of its degradation by esterases. Therefore it would be reasonable to assume that remifentanil may be a more suitable induction agent compared with other opiates. However, we found that neither remifentanil nor alfentanil could produce LOC consistently in all patients, even when administered in large doses over a 2-min period. Infusions of remifentanil ≤ 5 µg/kg and alfentanil ≤ 80 µg/kg did not produce LOC in any of the patients. In addition, increasing incidence and severity of muscle rigidity with increasing doses of both opioids further limited their utility as primary induction agents.

The ED₉₀ for LOC was estimated to be 12 µg/kg for remifentanil and 176 µg/kg for alfentanil. Based on the ED₉₀ for LOC, remifentanil appears to be approximately 15 times more potent than alfentanil. In a previous study by Glass et al, 1 remifentanil was estimated to be 20–30 times more potent than alfentanil for its analgesic and respiratory depressant properties when the study drugs were infused over 1 min. The difference in the potency ratios between the two studies may be due to the different endpoints measured. However, in both studies there was large variability among patients as evidenced by the range of the 95% CIs. Thus the 15–30 range of potency ratio may simply reflect the large pharmacodynamic variability seen with opioids.

When alfentanil is used to induce anesthesia in healthy unpremedicated patients, the ED₉₀ for loss of response to verbal command is 92 µg/kg and the ED₉₀ is 111 µg/kg. Nauta et al 6 reported that the LOC in healthy unpremedicated patients could be achieved at an average dose of 119 (SD ± 20) µg/kg when alfentanil was infused at a rate of 50 µg·kg⁻¹·min⁻¹. These doses
of alfentanil are lower than those that we determined. However, Silbert et al.\textsuperscript{9} could not induce anesthesia in 50% of their unpremedicated patients, even at an alfentanil dose of 200 \( \mu \text{g/kg} \), a finding that we confirmed in this study. A possible explanation for the difference in the \( \text{ED}_{\text{50}} \) for alfentanil is the rate at which alfentanil is administered. A more rapid injection would result in a higher peak effect site concentration and thus lower \( \text{ED}_{\text{50}} \) values. In addition, wide pharmacodynamic variability is observed when opioids are used to provide LOC, which could explain the discrepancy in the \( \text{ED}_{\text{50}} \) for LOC in these studies. Neither drug in our study could induce LOC reliably in all patients. This finding is consistent with the demonstration by other investigators that opioids can lower the minimum alveolar concentration of inhalational anesthetic agents but cannot function as sole anesthetic agents.\textsuperscript{10-12} Remifentanil at measured concentrations of 32 mg/ml reduces the minimum alveolar concentration of isoflurane by 90% and measured remifentanil concentrations of up to 60 mg/ml are associated with patient movement at skin incision.\textsuperscript{13} Our findings and those of Lang et al.\textsuperscript{13} suggest that remifentanil is not a suitable drug as a sole anesthetic either as an induction agent or as a maintenance agent.

The \( \text{EC}_{\text{50}} \) for LOC with remifentanil was 54 mg/ml, and for alfentanil it was 1,012 mg/ml. Thus, based on the \( \text{EC}_{\text{50}} \), remifentanil is approximately 19 times more potent than alfentanil. This potency ratio is similar to the potency ratio of 16 determined by Egan et al.\textsuperscript{4} using the electroencephalograph as a surrogate measure of opioid effect. Using reduction of the minimum alveolar concentration of isoflurane as an endpoint, remifentanil whole-blood concentration is 70 times more potent than alfentanil plasma concentration (or 40 times more potent than alfentanil whole-blood concentration).\textsuperscript{15} This discrepancy in potency ratio may be due to different measured endpoints and pharmacodynamic variability.

The large doses of opioid required to provide LOC also resulted in muscle rigidity, which was a significant clinical problem despite prior administration of a small dose of d-tubocurarine. Muscle rigidity is well known with a large dose of opioids.\textsuperscript{15,16} This study also confirms that there is a dose-dependent increase in both the incidence and severity of muscle rigidity with opioids.

Remifentanil produced a dose-independent decrease in blood pressure just before intubation from the baseline values. The decrease in blood pressure was mild, and no patient required ephedrine for treatment. Thus both drugs when given on their own, even at large doses, provide acceptable hemodynamic stability in healthy patients. Alfentanil was more effective than remifentanil in ablating the response to intubation. The more rapid decrease in blood concentration of remifentanil by the time intubation was undertaken (71% vs. 47%) may explain its relative ineffectiveness in modifying the response to laryngoscopy and intubation. The implication of this finding is that, if remifentanil is used in a single dose at induction, an additional dose may be required just before intubation to blunt the response to this stimulus. Alternatively, infusion of this opioid should be initiated before intubation.

In conclusion, administration of alfentanil and remifentanil as 2-min infusions in healthy, unpremedicated patients does not reliably produce LOC. In addition, a dose-dependent increase in the incidence and severity of muscle rigidity with these opioids is an important clinical problem. Remifentanil is 15 times more potent than alfentanil based on the \( \text{ED}_{\text{50}} \) for loss of response to verbal command and 19 times more potent than alfentanil based on the whole-blood concentrations. We observed an extremely rapid decrease in remifentanil
concentrations and recommend that an additional dose of the drug should be administered before intubation to obtund the hemodynamic response to laryngoscopy.

References


11. Murphy MR, Hug CC: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982; 57:485--88


