

Assessment of Depth of Anesthesia and Postoperative Respiratory Recovery after Remifentanyl- versus Alfentanil-based Total Intravenous Anesthesia in Patients Undergoing Ear–Nose–Throat Surgery

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Background: The authors investigated whether total intravenous anesthesia (TIVA) with precalculated equipotent infusion schemes for remifentanyl and alfentanil would ensure appropriate analgesia and that remifentanyl would result in better recovery characteristics.

Methods: Forty consenting patients (classified as American Society of Anesthesiologists physical status I–III) scheduled for microlaryngoscopy were randomized to receive, in a double-blind manner, either remifentanyl (loading dose $1 \mu\text{g}/\text{kg}$; maintenance infusion, $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or alfentanil (loading dose, $50 \mu\text{g}/\text{kg}$; maintenance infusion, $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) as the analgesic component of TIVA. They were combined with propofol (loading dose, $2 \text{ mg}/\text{kg}$; maintenance infusion, $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). To insure an equal state of anesthesia, the opioids were titrated to maintain heart rate and mean arterial pressure within 20% of baseline, and propofol was titrated to keep the bispectral index (BIS) less than 60. Neuromuscular blockade was achieved with succinylcholine. Drug dosages and the times from cessation of anesthesia to extubation, verbal response, recovery of ventilation, and neuropsychological testing, orientation, and discharge readiness were recorded.

Results: Demographics, duration of surgery, and anesthesia were similar between the two groups. Both groups received similar propofol doses. There were no difference in BIS values preoperatively (mean, 96), intraoperatively (mean, 55), and postoperatively (mean, 96). Recovery of BIS and times for verbal response did not differ. At 20, 30, and 40 min after terminating the opioid infusion, the peripheral oxygen saturation and respiratory rate were significantly higher in the remifentanyl group compared with the alfentanil group.

Conclusions: When both the hypnotic and analgesic components of a TIVA-based anesthetic are administered in equipotent doses, remifentanyl provides a more rapid respiratory recovery, even after brief surgical procedures, compared with alfentanil.

WITH the introduction of new potent anesthetics (sevoflurane, desflurane, propofol) and analgesics (remifentanyl) into contemporary clinical anesthesia practice, it is important to validate the advantages of regimens using these compounds to provide optimal

anesthesia.¹⁻³ Preclinical and clinical studies indicated that remifentanyl, a new esterase-metabolized μ -opioid, provides analgesia and a rapid decrease in drug concentration because of its unique pharmacokinetics. It was therefore proposed that the use of remifentanyl allow for a more rapid recovery compared with other opioids. Total intravenous anesthesia (TIVA) has gained a new interest with the clinical availability of remifentanyl. However, the coadministration of a potent analgesic alters the plasma concentration of the coadministered hypnotic required to provide loss of consciousness (LOC) and prevention of movement to skin incision.⁵⁻⁷ Thus, the use of different opioids for TIVA implies complex pharmacology.⁶ To establish any differences in recovery profile between opioids, it is critical that the same degree of hypnosis is achieved when making comparisons. In addition, when using opioids in high concentrations, clinical signs of awareness might be masked. Thus, monitoring of the state of consciousness appears to be necessary.⁸ Conventional clinical signs in enabling anesthetists to recognize periods of conscious awareness may be less reliable with the administration of remifentanyl to maximal analgesic concentrations.⁹ The bispectral index (BIS), a derived value of the electroencephalogram, has become a reliable measure for LOC and loss of recall for volatile and intravenous agents.¹⁰⁻¹³ The present study was designed to test the hypothesis that TIVA with precalculated equipotent infusion scheme for remifentanyl and alfentanil would ensure appropriate analgesia, and an equal state of LOC and remifentanyl administration would result in better recovery characteristics.

Methods

After institutional review board approval from Wilhelms-Universität Münster and informed consent were obtained, 42 patients classified as American Society of Anesthesiologists physical status I–III who were scheduled for microlaryngoscopy were enrolled in the study. Exclusion criteria were age younger than 18 yr or older than 70 yr, use of analgesics or sedatives within the previous 24 h before the study, a known pseudocholinesterase deficiency, and failure at the time of the preoperative interview to complete a series of neuropsychological function tests as described below. Patients

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Received from the Klinik und Poliklinik für Anästhesiologie und operative Intensivmedizin, Westfälische Wilhelms-Universität Münster, Münster, Germany, and the Department of Anesthesiology, State University of New York-Stony Brook, Stony Brook, New York. Submitted for publication July 8, 1999. Accepted for publication August 21, 2000. Support was provided solely from institutional and/or departmental sources.

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were also excluded if they were more than twice ideal body weight, significantly hypertensive (diastolic blood pressure > 100 mmHg) or hypotensive (systolic blood pressure < 100 mmHg), or presented any previous signs of bradyarrhythmic heart disorders.

Patients were prospectively studied and assigned in a randomized, double-blind manner to one of two treatment groups: (1) intravenous remifentanyl (loading dose, 1.0 $\mu\text{g}/\text{kg}$ over 120 s; maintenance, 0.25 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$); or (2) intravenous alfentanil (loading dose, 50 $\mu\text{g}/\text{kg}$ over 120 s; maintenance, 1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). These infusion schemes were determined through pharmacokinetic simulations to achieve equipotent opioid concentrations based on a potency ratio of 1 ng/ml (plasma) remifentanyl equivalent to 40 ng/ml (whole blood) alfentanil. The dilution of remifentanyl was 3 mg/50 ml and for alfentanil 12 mg/50 ml, which provided equal infusion rates for maintenance in both groups. No premedication was given. Standard monitoring included continuous heart rate *via* electrocardiogram, noninvasive blood pressure obtained every 1–5 min, and continuous pulse oximetry. An electroencephalogram signal was obtained using electrodes applied in a bifrontal montage (Fp1–A1 and Fp2–A2 in the International 10–20 System of electrode placement). Impedance was less than 5 k Ω . The BIS value was displayed using an Aspect electroencephalogram monitor (Model A-1050; Aspect Medical Systems, Natick, MA). An interviewer who was not aware of the study drug (supplied as coded bolus and infusion syringes) recorded all perioperatively obtained measurements at 1-min intervals during induction of anesthesia and subsequently at 2–5-min intervals during the maintenance period. They also performed all tests in the postoperative anesthetic care unit (PACU). On arrival in the operating room, the baseline values for BIS, heart rate, blood pressure, and pulse oximetry were obtained, and an intravenous catheter was placed. Before induction of anesthesia, patients breathed 100% oxygen for 5 min and were given 5 ml/kg intravenous fluid (*e.g.*, lactated Ringer's solution). Before delivery of a loading bolus of remifentanyl or alfentanil (over 120 s), 0.5 mg atropine was injected. The continuous infusion of remifentanyl or alfentanil was started at a rate of 0.25 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for remifentanyl or 1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for alfentanil. Induction bolus of propofol (2 mg/kg) was injected simultaneously with the analgesic and continued at 100 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ throughout the procedure. Once LOC (no verbal response) was achieved, a succinylcholine infusion was started at a maintenance dose of 100 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Oxygen was delivered concomitantly *via* face mask until endotracheal intubation was performed using a special high-frequency jet ventilation tube. All patients were mechanically ventilated using a high-frequency jet ventilation technique. Inspiratory oxygen concentration was maintained to achieve adequate levels of oxygen saturation ($\text{SpO}_2 > 93$). Blood pressure, heart rate, SpO_2 ,

Table 1. Vigilance Scores after Camron

0 = No reaction
1 = Unspecific body movements
2 = Unspecific mimic motions
3 = Eye opening
4 = Directed eye movements
5 = Hand shaking
6 = Telling residency
7 = Telling age and date of birth
8 = Completion of interference task
9 = Recognition of complex graphic pattern
10 = Drawing of pattern

and BIS were monitored and recorded at 1-min intervals during induction of anesthesia and subsequently at 5-min intervals throughout anesthesia.

Inadequate hypnosis was defined as BIS greater than 60 and was treated with a bolus dose of propofol 1 mg/kg. Inadequate analgesia was defined as responses to surgical stimuli by hypertension (systolic blood pressure > 20% above preoperative baseline value for more than 5 min) or tachycardia (heart rate > 20% above preoperative baseline values).

Responses were initially treated by administering one or two bolus doses of study drug (remifentanyl group = 0.5 $\mu\text{g}/\text{kg}$; alfentanil group = 4 $\mu\text{g}/\text{kg}$). If this treatment was unsuccessful, the study drug infusion rate was doubled. Hypotension (mean arterial pressure < 60 mmHg) was treated by fluid delivery (5 ml/kg intravenous lactated Ringer's solution) or vasopressor if this treatment was ineffective. To assess intraoperative awareness, in addition to a standard interview obtained postoperatively to elicit any recall events during anesthesia, a number was repetitively told to each patient four times during anesthesia at 5, 10, 15, and 20 min by the observer. The patient was specifically questioned for recall of this number.

At the end of surgery, all infusions were terminated and 100% oxygen was applied through the high-frequency jet ventilation tube until the return of spontaneous respiration. The trachea was then immediately extubated. The patient received oxygen delivered *via* an open face mask with a flow of 4 l/min for the next 5 min. Recovery times were determined in 1-min intervals from cessation of the TIVA delivery until the patient qualified for transfer to the PACU. In the PACU, criteria for discharge were evaluated every 2–5 min. There was

Table 2. Demographics and Operation Times

Group	Remifentanyl	Alfentanil	U Test
Sex (M/F)	17/3	15/5	
Height (cm)	174 \pm 8	170 \pm 7	NS
Weight (kg)	78 \pm 15	75 \pm 11	NS
Age (yr)	52 \pm 12	57 \pm 8	NS
Duration of surgery (min)	19 \pm 9	24 \pm 13	NS
Anesthesia (min)	30 \pm 9	34 \pm 13	NS

NS = not significant.

Table 3. Drug Consumption and Postoperative Recovery

Group	Remifentanil	Alfentanil	U Test
Dose of analgesic ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	0.28 ± 0.02	2.9 ± 0.6	
Propofol boli	13	12	NS
Dose of propofol ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	173 ± 24	166 ± 22	NS
Spo ₂ (at 20 min after surgery)	98 ± 2	95 ± 3	$P < 0.05$
Respiratory rate (count/min at 20 min after surgery)	16 ± 4	12 ± 3	$P < 0.05$
Patients with Aldrete score of 10 after 10 min	79%	40%	$P < 0.05$
Patients with Aldrete score of 10 after 30 min	95%	65%	$P < 0.05$
Nausea	1	1	
Pruritus	1	3	
Shivering	1	0	

NS = not significant; Spo₂ = oxygen saturation measured by pulse oximetry.

no oxygen supplied if not indicated (Spo₂ < 90%). During the recovery period, patients had to complete a vigilance test (Camron test¹⁴) to evaluate their psychometric and psychomotor function. This test consists of 10 different graded tasks displayed in table 1. Each task follows one after the other, if they are completed adequately. The Camron test is summarized as a score of vigilance, with 0 being unconscious and 8–10 absolutely alert. To gain reproducible scores, each patient was introduced to the test the day before surgery with similar, but not the same, tasks. Patients failing to complete the test or with baseline values less than 8 were excluded from the study. In addition, Aldrete scores were recorded concomitantly, and BIS were monitored until actual discharge from the PACU.

Recovery included the time from the end of surgery until achievement of adequate respiratory function and time until adequate completion of psychomotor and psychometric tests defined as a Camron score greater than 8 and an Aldrete score greater than 9. Secondary end points of this study were the comparison of BIS indices and hemodynamic responses to stimuli for the two distinct TIVA schemes. Using pharmacokinetic simulations (<http://pkpd.icon.palo-alto.med.va.gov/>), we determined the predicted plasma concentrations for remifentanil and alfentanil based on previously published pharmacokinetic parameters for each study patient after completion of the study.

Statistical analysis included the Kolmogorov-Smirnov test for all data. Analysis of variance followed by *post hoc* analysis (Scheffé test) and Mann-Whitney U test were used as appropriate. A Wilcoxon test was performed for respiratory rate and pulse oximetry. All tests were performed with commercially available statistic software (SPSS Inc., Chicago, IL). In all tests, a *P* value less than 0.05 was considered to be significant. Before the study, we performed a power analysis with previously obtained data at our institution to assess the sample size required to detect a difference of 30% time to achieve an Aldrete score of 8 or greater. This suggested a sample size of 15 patients for each group (power of 0.81 α 0.05).

Results

A total of 42 patients were enrolled in the study. One patient was withdrawn because of a severe asthmatic episode after cessation of the study drug (alfentanil) that

Calculated plasma levels for Remifentanil and Alfentanil

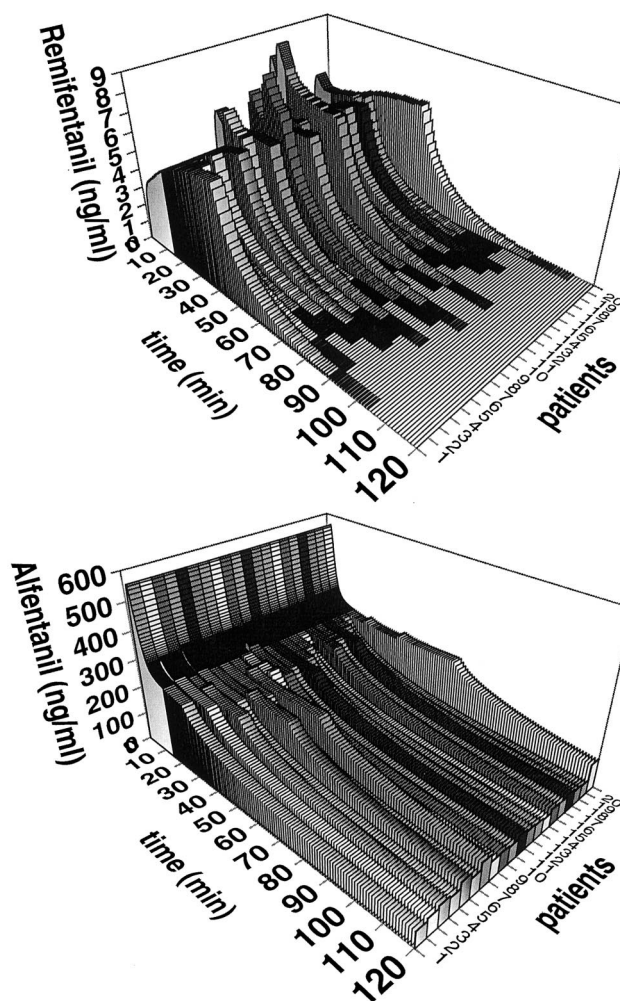


Fig. 1. Data displaying the individual plasma concentrations for remifentanil (*top*) and alfentanil (*bottom*), using pharmacokinetic simulations.

Hemodynamics: TIVA with Remifentanyl or Alfentanil

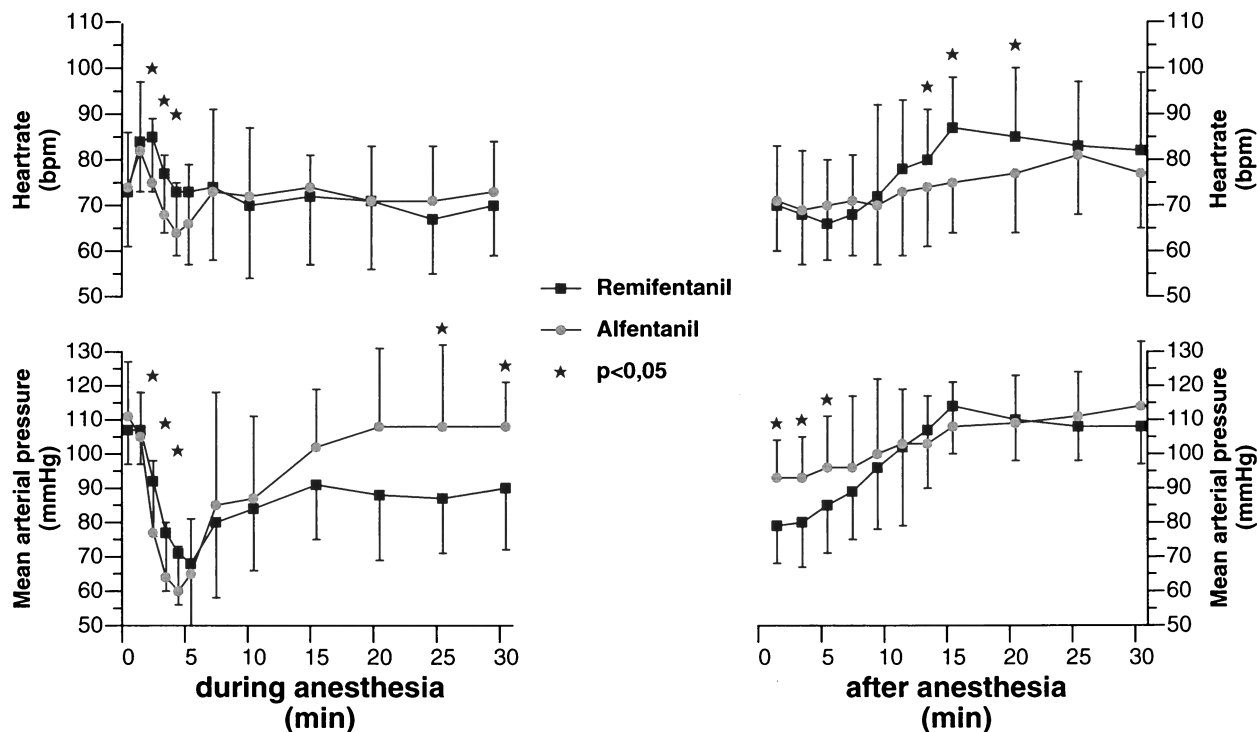


Fig. 2. (Top) Data displays the mean heart rate in beats per minute (bpm) on the y-axis in patients receiving total intravenous anesthesia (TIVA) with either remifentanyl (black squares; $n = 20$) or alfentanil (grey circles; $n = 20$). Values are mean \pm SD. On the left of the x-axis, the time course from start of anesthesia until termination of TIVA is displayed in minutes (at 5 min, endotracheal intubation was performed); on the right, the time course for the heart rate from 1 min after cessation of the TIVA until discharge from the postanesthesia care unit is displayed. The asterisks indicate differences in the heart rate at the distinct time points between remifentanyl and alfentanil groups ($P < 0.05$). (Bottom) Data showing the mean arterial pressure (MAP) in patients who received TIVA with either remifentanyl (squares; $n = 20$) or alfentanil (circles; $n = 20$). Values are mean \pm SD. On the left of the x-axis, the time course from start of anesthesia until termination of TIVA is displayed in minutes (at 5 min, endotracheal intubation was performed); on the right, the time course for MAP from 1 min after cessation of TIVA until discharge from the postanesthesia care unit is displayed. The asterisks indicate differences in MAP at the distinct time points between remifentanyl and alfentanil group ($P < 0.05$).

required pharmacologic intervention, and another patient was withdrawn because of inability to complete the psychometric and psychomotor tests at the presurgical interview. Thus, data of 40 patients were analyzed. The two treatment groups were comparable with respect to the demographic data, American Society of Anesthesiologists physical status, and duration of surgery and anesthesia (table 2).

Both groups required a similar total dose of intravenous propofol (table 3; $P > 0.05$). There was also no statistical significant difference with respect to the total dose of intravenous succinylcholine.

Simulations revealed remifentanyl concentrations were more variable compared with alfentanil (fig. 1). However, there was a faster decay in drug plasma concentration with cessation of infusion for remifentanyl versus alfentanil (fig. 1).

Mean arterial pressure decreased by $37 \text{ mmHg} \pm 11$ (\pm SD) in the remifentanyl group after induction compared with $45 \pm 5 \text{ mmHg}$ in the alfentanil group ($P < 0.05$). By 10 min after induction there was a greater

increase in mean arterial pressure in the alfentanil group compared with the remifentanyl group ($P < 0.05$; fig. 2 bottom). However, both groups revealed hemodynamic within an acceptable clinical range.

Mean heart rate changed by 8 ± 12 beats/min for remifentanyl and by 14 ± 14 beats/min for alfentanil (fig. 1). Heart rates differed between remifentanyl- and alfentanil-treated patients within the first 3 min after start of induction and from 10–20 min after the infusion had been stopped (fig. 2, top).

Time until extubation was not different for both groups (remifentanyl, 9 ± 2 min; alfentanil, 11 ± 5 min; $P > 0.05$). Respiratory rates and SpO_2 values revealed a significantly faster recovery for remifentanyl-treated patients compared with the alfentanil group. Within the first 40 min after termination of the opioid infusion, remifentanyl-treated patients had returned to preoperative respiratory rates, whereas alfentanil-treated patients had lower respiratory rates and SpO_2 (fig. 3).

The preoperative BIS index baseline values were similar in both groups (mean, 96 ± 2 SD). This index

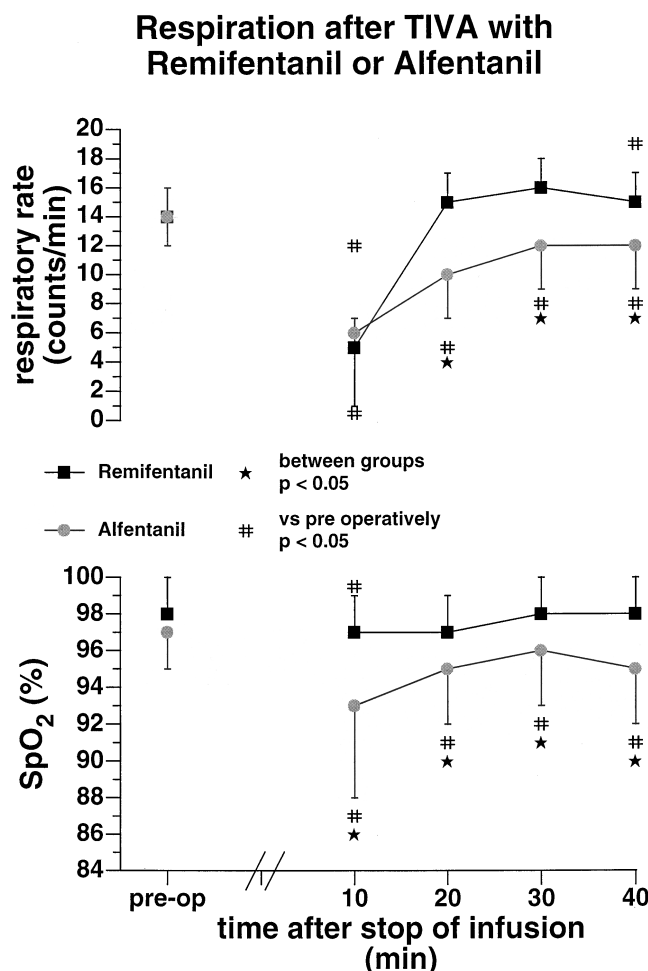


Fig. 3. (Top) Data displaying the respiratory rate per minute on the y-axis in patients receiving total intravenous anesthesia (TIVA) with either remifentanil (black squares; $n = 20$) or alfentanil (grey circles; $n = 20$). Values are mean \pm SD. (Bottom) Data displaying pulse oximetry values on the y-axis in patients receiving TIVA with either remifentanil (black squares; $n = 20$) or alfentanil (grey circles; $n = 20$). Values are mean \pm SD. On the x-axis for both graphs, preoperative baseline values are displayed, followed by the observed values after termination of TIVA in minutes. The asterisks indicate differences at the distinct time points between remifentanil and alfentanil, and the number signs indicate differences versus the preoperatively assessed baselines ($P < 0.05$).

decreased within the first 3 min after induction to values of 52 ± 10 (remifentanil) or 54 ± 12 (alfentanil) and remained at similar values throughout the maintenance period (fig. 4 and table 3). There was no significant difference between groups at any distinct time. After termination of TIVA delivery, both groups revealed a similar increase in the recovery of their BIS indices (recovery within 13 min for remifentanil and within 12 min for alfentanil; $P > 0.05$; fig. 4).

The assessment of postoperative psychometric and psychomotor function using a vigilance score (Camron test) showed no significant difference in the recovery of neuropsychological function with remifentanil-treated patients (remifentanil: score > 8 , 14 ± 5 min; alfentanil:

20 ± 11 min; fig. 5). In addition, there was a significant difference in obtaining an Aldrete score of 10 (at 10 min, 79% of remifentanil patients and 40% of alfentanil patients; at 30 min, 95% of remifentanil patients and 65% of alfentanil patients; $P < 0.05$).

Vomiting was observed only in one patient in each group, pruritus was experienced by three alfentanil patients and one remifentanil patient, and shivering was experienced by one remifentanil patient.

Discussion

The present study investigated the recovery profile of a TIVA technique with equipotent infusion schemes for the two short-acting μ -opioids, remifentanil and alfentanil, while maintaining intraoperatively a similar degree of hypnosis in both groups. TIVA with remifentanil resulted in a superior recovery profile compared with an alfentanil-based TIVA, as shown by a more rapid recovery of ventilatory function and higher Aldrete scores at 10 and 30 min. This more rapid recovery is likely to be caused by the unique esterase metabolism of remifentanil that results in a very rapid decay in its blood concentration (fig. 1).

The theoretical advantage of remifentanil is that it can be administered at maximal analgesic efficacy during surgical procedure but still enable a rapid recovery and return of adequate spontaneous ventilation.¹⁵⁻¹⁷ Micro-laryngoscopy is a surgical procedure requiring intense analgesia and rapid recovery and thus should be an ideal procedure in which to use the properties of remifentanil. Alfentanil also has a rapid onset and can provide intense analgesia but, based on its context-sensitive decay times, would be predicted to provide slower recovery of respiratory function, especially when given for a procedure requiring more than a single bolus dose.¹⁸ In addition, alfentanil displays considerable variability in its pharmacokinetics because of its hepatic metabolism.¹⁹ Numerous studies to date have compared remifentanil to alfentanil, but none has attempted to administer them at equipotent concentrations and then evaluate recovery for both drugs.^{20,21} Although the brief duration of the procedure used in our experimental design might not be the optimal condition to elucidate differences of both opioids in terms of the speed of recovery, the observed differences already suggest even more distinct discrepancies for prolonged procedures.²²

Recent research focusing on the pharmacologic interaction between anesthetics and opioids has revealed complex pharmacokinetic and pharmacodynamic interactions.^{5,6} Increasing opioid concentration decreases the concentration of propofol required to prevent movement at skin incision in a nonlinear interaction. Recovery after a combination of propofol and opioid is dependent on the propofol reaching its wake-up concentration and

Bispectral Indices in TIVA with Remifentanyl or Alfentanil

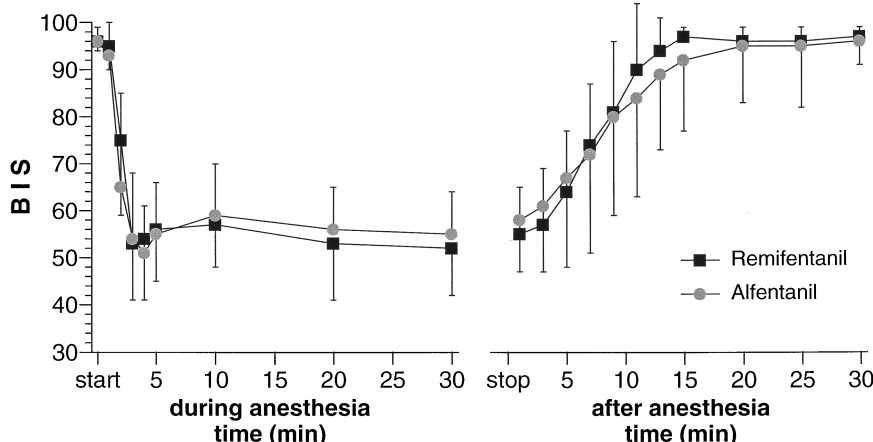


Fig. 4. Data showing the assessment of depth of anesthesia by bispectral indices (BIS), recorded in patients who received total intravenous anesthesia (TIVA) with either remifentanyl (squares; n = 20) or alfentanil (circles; n = 20) and displayed as BIS on the y-axis. Values are mean ± SD. On the left of the x-axis, the time course from start of anesthesia until termination of TIVA is displayed in minutes (at 5 min, endotracheal intubation was performed); on the right, the time course for the BIS from 1 min after cessation of the TIVA until discharge from the postanesthesia care unit is displayed. There were no statistical significant difference in BIS at the distinct time points between remifentanyl and alfentanil groups ($P < 0.05$).

the opioid decreasing to a concentration below which adequate ventilation occurs. Thus, when evaluating recovery from a TIVA technique, it is important to insure that both the opioid and the hypnotic is administered to equivalent effect in both groups. These complexities may have limited the ability to perform such comparative studies.

Bispectral analysis is a quantitative technique that measures the consistency of the phase and power relations of the electroencephalogram signals derived, and it re-

turns a single number, the BIS.⁸ The BIS has been shown to predict LOC and loss of recall for volatile and intravenous anesthetics. An index value less than 60 correlated with LOC and loss of recall in 95% of patients.¹² For both analgesics, remifentanyl and alfentanil, recent reports indicate that reliable LOC is not achievable when they are administered alone.²³ Thus, a hypnotic drug is required when using these opioids to ensure adequate anesthesia. The contribution of the hypnotic to the anesthetic state can be determined using the BIS. Using precalculated dosing schemes, based on pharmacokinetic parameters from previous studies,²⁴ we calculated that the propofol rate administered will result in plasma concentrations of propofol of $2.2-2.9 \pm 1.2 \mu\text{g/ml}$ over a 30-min infusion period. This concentration of propofol is associated with LOC when combined with the analgesic concentrations of the opioid used in this study. By ensuring that propofol achieved equal BIS values in both groups, the difference in recovery from anesthesia was dependent on the concomitant opioid.

The second factor in providing appropriate comparisons between opioids is to insure they are administered at equipotent concentrations. Several investigators have tried to establish the relative potency of remifentanyl to alfentanil. As we were observing their action in a balanced anesthetic technique, we based our relative potency on their ability to reduce the minimum alveolar concentration of isoflurane. Based on this estimate, remifentanyl (blood concentration) is 40 times more potent than alfentanil (plasma concentration).²⁵ This was also recently confirmed in another comparative study with remifentanyl and alfentanil using ventilatory depression as the measure of opioid effect,²⁶ and thus equipotent infusion schemes were used in our study.

In a recently reported comparison of remifentanyl and alfentanil in coadministration with isoflurane in outpatient surgery, alfentanil displayed a more favorable profile compared with remifentanyl with regard to recovery

Postoperative vigilance score (Camron test) in TIVA with Remifentanyl or Alfentanil

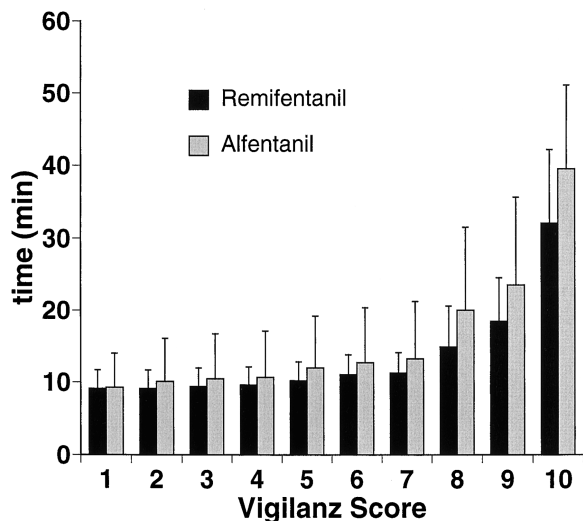


Fig. 5. Bars represent the mean time (minutes on the y-axis) in the two total intravenous anesthesia (TIVA) groups (remifentanyl, solid bars, n = 20; alfentanil, grey bars, n = 20) until a distinct level of the Camron test, displayed on the x-axis as the Vigilanz score from 0 (unconscious) to 10 (completion of complex drawing tasks), was achieved.

of verbal responsiveness, adequate respiration, and tracheal extubation.²⁷ However, the applied dosing scheme of alfentanil 25 $\mu\text{g}/\text{kg}$ as bolus dose and 0.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ as infusion would be below our calculated lower range of an alfentanil plasma concentration that was equipotent with their remifentanil dosing scheme. This was supported by the higher incidence of supplemental analgesic injections in the alfentanil group in this study.²⁷

In conclusion, we present a study in which we compared the intraoperative and recovery profile after the equipotent administration of remifentanil to alfentanil during brief ear-nose-throat procedures. We found that the intraoperative course was similar, but respiratory recovery was more rapid with remifentanil. These findings would imply that for brief procedures with intense noxious stimulation, remifentanil may be the opioid of choice, especially if rapid respiratory recovery is mandatory.

The authors thank Aspect Medical Systems, Space Lab, Germany, for providing the bispectral index monitor and disposable electrodes; and Döring Technology, Germany, for providing the infusion pump system.

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