

Determination of the Potency of Remifentanyl Compared with Alfentanil Using Ventilatory Depression as the Measure of Opioid Effect

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Background: Remifentanyl is a new opioid with properties similar to other mu-specific agonists. To establish its pharmacologic profile relative to other known opioids, it is important to determine its potency. This study investigated the relative potency of remifentanyl compared with alfentanil.

Methods: Thirty young healthy males were administered double-blind remifentanyl or alfentanil intravenously for 180 min using a computer-assisted continuous infusion device. Depression of ventilation was assessed by the minute ventilatory response to 7.5% CO₂ administered *via* a "bag in the box" system. The target concentration of the study drug was adjusted to obtain 40–70% depression of baseline minute ventilation. Multiple blood samples were obtained during and following the infusion. The concentration–effect relationship of each drug was modeled, and the concentration needed to provide a 50% depression of ventilation (EC₅₀) was determined.

Results: Only 11 subjects in each drug group completed the study; however, there were sufficient data in 28 volunteers to model their EC₅₀ values. The EC₅₀ (mean and 95% confidence interval) for depression of minute ventilation with remifentanyl was 1.17 (0.85–1.49) ng/ml and the EC₅₀ for alfentanil was 49.4 (32.4–66.5) ng/ml.

Conclusion: Based on depression of the minute ventilatory response to 7.5% CO₂, remifentanyl is approximately 40 (26–

65) times more potent than alfentanil when remifentanyl and alfentanil whole-blood concentrations are compared. As alfentanil is usually measured as a plasma concentration, remifentanyl is approximately 70 (41–104) times more potent than alfentanil when remifentanyl whole-blood concentration is compared with alfentanil plasma concentration. This information should be used when performing comparative studies between remifentanyl and other opioids. (Key words: Analgesics; computers; pharmacodynamics; pharmacokinetics.)

REMIFENTANIL is a new anilidopiperidine analogue recently approved in several countries as an adjunct for the induction and maintenance of general anesthesia. Its structure contains an ester side-chain linkage that is subject to esterase metabolism.¹ This results in an opioid with unique pharmacokinetic parameters that provide an ultrashort-lasting drug.^{2–4} Its pharmacologic properties appear similar to other potent mu-specific opioids.⁵ When evaluating such a new compound for clinical practice, it is important to establish its potency relative to other analgesics so that comparisons can be made to other known opioids at equieffective doses or concentrations. This concept is similar to establishing the minimum alveolar concentration (MAC), which prevents movements in 50% of patients following a supramaximal stimulus, prior to describing and comparing the pharmacology of a new volatile anesthetic.⁶

To establish the potency of a drug, it is critical to have a measure of its effect that is sensitive and specific and provides a concentration-dependent change within the clinical range. For an opioid, the obvious measure of effect is pain relief from a noxious stimulus. Pain relief is a subjective measure with wide patient-to-patient variability. In addition, although there are many models to provide a noxious stimulus, the efficacy of many of these stimuli in producing a reliable and reproducible painful event has been questioned.⁷ Thus, the use of pain relief as a measure of drug effect is difficult and may be unreliable. Potent mu-opioids not only result in dose-dependent analgesia but also result in similar dose-de-

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pendent ventilatory depression.⁴ Ventilatory depression is an objective measure, can be readily quantified, and occurs within the clinical range of analgesia. Thus, a measure of ventilatory depression can be used as a measure of opioid effect. The potency of any drug may be determined in terms of either a single dose, an infusion rate, or a drug concentration. The potency relative to another opioid differs for each of these measures because of differences in their disposition. The potency of remifentanyl relative to alfentanil following a single bolus dose has been established.⁴ As remifentanyl is such a short-lasting drug, it is unlikely to be frequently used as a single bolus dose. With the advent of target-controlled drug delivery, wherein a physician-specified concentration can be targeted, establishment of potency in terms of drug concentration (which has been equilibrated with the drug's biophase) is important.⁸ From this, the infusion profile required to provide these concentrations can also be determined. Thus, we wished to establish the relative potency of remifentanyl to alfentanil in terms of drug concentration using depression of ventilation drive as the measure of effect.

Methods

Approval was obtained from Duke University Medical Center's Institutional Review Board for human subjects. Thirty paid volunteers were recruited, and all gave written informed consent. Inclusion criteria were healthy (having American Society of Anesthesiologists physical status I or II) males between 18 and 40 yr of age, weighing less than 100 kg and within 20% of ideal body weight. Exclusion criteria included a history of allergy to opioids, exposure to opioids or anesthesia within 60 days of the study, and a history of alcohol or drug abuse. Volunteers were also excluded if they smoked more than 10 cigarettes per day, were on any chronic medications, or had taken any over-the-counter medications within 3 days of the study. All volunteers were asked to abstain from beverages containing caffeine 24 h prior to the study and were instructed to remain *nil per os* for 12 h prior to the study. Subjects were screened within 1 week of the study, at which time histories were taken and physical examinations performed. Blood was also drawn at this visit to obtain hematologic values and clinical chemistries. Urine samples were obtained for blood chemistries and detection of illicit drugs. A 12-lead electrocardiogram (ECG) was also obtained prior to the study. These data on all subjects were found to be within

Table 1. Pharmacokinetic Parameters Used in CACI

Pharmacokinetic Parameter	Alfentanil	Remifentanyl
K10 (/min)	0.091	0.376
K12 (/min)	0.656	0.309
K21 (/min)	0.214	0.192
K13 (/min)	0.113	NA
K31 (/min)	0.017	NA
V1 (l/kg)	0.03	0.12

CACI = computer-assisted continuous infusion; NA = not applicable.

the normal clinical range prior to admission to the study. Volunteers were trained in the use of the "bag in a box" system, which was utilized to evaluate minute ventilatory response to 7.5% inspired CO₂.⁹ Following this training session, a 5-min run was performed, as described subsequently.

On the morning of the study, the subject was placed in a quiet and darkened room. A catheter was inserted into the radial artery and a peripheral vein. A nasal cannula, ECG pads, and a pulse oximeter finger probe were also placed. Arterial blood pressure, end-tidal CO₂, respiratory rate, finger peripheral hemoglobin oxygen saturation (SpO₂), ECG (lead II), and heart rate were continuously monitored and recorded *via* the monitor's RS232 port to a computer-based data-acquisition system.

The subjects, in the randomized double-blind, double-dummy manner, received either remifentanyl or alfentanil. Blinding was achieved by having the hospital pharmacy prepare two infusion bags, one labeled as remifentanyl and the other labeled as alfentanil. For each subject, one infusion bag contained active drug and the other bag contained normal saline. Following baseline measurements, both bags were attached to a computer-assisted continuous infusion device¹⁰ for 180 min and were administered as though each contained active drug. The initial targets were for remifentanyl a whole-blood concentration of 1 ng/ml and for alfentanil a plasma concentration of 80 ng/ml. These concentrations were estimated to be equipotent using effect compartment modeling from a previous study.⁴ The pharmacokinetic model parameters used in computer-assisted continuous infusion for this study are listed in table 1. For remifentanyl, they were from the very first study in humans.⁴ The pharmacokinetic parameters of Scott *et al.*¹¹ were used for alfentanil.

Minute ventilation (MV) at steady state end-tidal 7.5% CO₂ using a bag-in-a-box system was used as a measure of drug effect.^{12,13} The volunteer patient was attached *via* a tight-fitting face mask to the bag-in-a-box system

Table 2. The Adjustment in the Target Concentration Made to Obtain a 40–70% Decrease from Baseline of Minute Ventilation when Breathing 7.5% Carbon Dioxide

Decrease in Minute Ventilation (%)	Target Serum Concentration Multiplied By
0–20	2
21–30	1.5
31–39	1.2
40–70	No change
71–80	0.8
81–90	0.5
>91	0.2

equilibrated with 7.5% CO₂, nitrogen and oxygen for 5 min. The inspired CO₂ of the system is maintained constant by manually varying flow through a bypass limb that is attached to a CO₂ scrubber. The initial 4 min of each MV run allowed time for equilibration of the inspired CO₂ and the respiratory center in the brain (*i.e.*, in the first 3 min MV increases as equilibration occurs, but by the fourth minute, MV is constant). The MV data reported include the average of the recorded MV integrated over each 15-s interval measured in the last (5th) minute. MV was measured at 15 and 30 min prior to drug infusion. The resultant MV was compared between these two time intervals and the initial training MV to ensure they were all within 20% of each other to confirm consistency. Following the initiation of drug administration, MV was measured at 15 min, when it was assumed (based on the published k_{e0} values for remifentanyl and alfentanil)^{3,4,14} that equilibration between target concentration and the biophase had been obtained. If the MV depression was outside the desired range of 40–70% of the baseline MV, the target concentrations of both drugs

were simultaneously adjusted, as listed in table 2. MV was then measured every 15 min after the beginning of the drug infusion until successive measurements were within 40–70% of the subjects' baseline MV and within 20% of each other. Thereafter, MV was measured every 30 min and at 170 min. Subjects requiring more than two adjustments in the target concentration of the opioid within the first 60 min of the infusion were withdrawn from the study.

Arterial blood samples were obtained at 30 min prior to drug administration and then at 15, 30, 45, 60, 90, 120, 150, and 170 min following the initiation of drug administration. If the target concentration needed to be adjusted so as to alter the volunteers' MV within the targeted percentage depression, then further blood samples were collected just prior to the change in the target drug concentration and 1, 3, 5, 10, 15, and 20 min after the change in target concentration. Previously scheduled samples during this period were not collected. Arterial blood samples for blood gas determination were also taken at 15 and 30 min prior to initiation of the infusion and at 15, 30, 45, 60, 90, 120, 150, and 170 min after starting the infusion. The study design is shown in figure 1.

From 2 min prior to terminating the infusion until 10 min after the end of the infusion, subjects were maintained on the bag-in-a-box system, with the MV for each minute being recorded. This provided MV measurements for each of the first 10 min following termination of drug infusion. MV measurements (as previously described) were made at 20 min, at 30 min, and every 15 min thereafter until values returned to baseline. Blood samples were also obtained after the termination of the

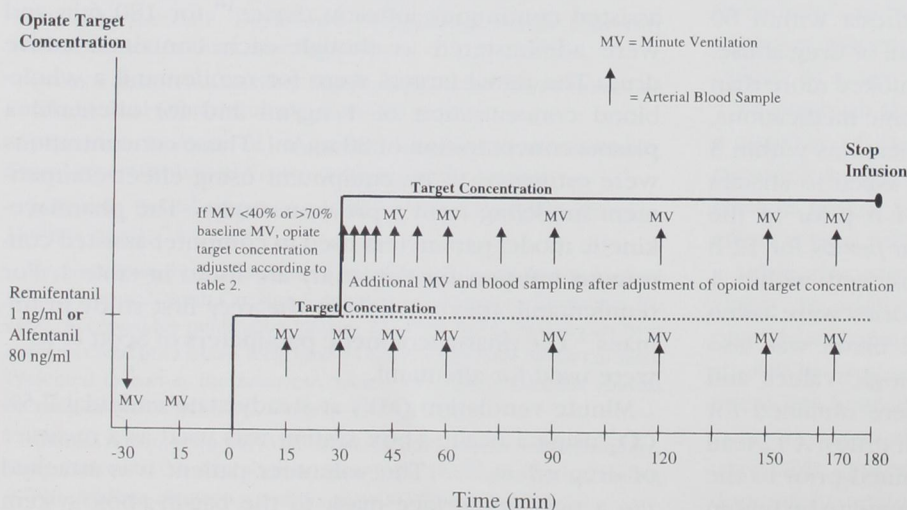


Fig. 1. Study design showing the times of minute ventilation (MV) and arterial blood sampling for arterial blood gas determination and opioid concentration, before and after the beginning of the drug infusion and after an opioid target concentration adjustment.

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drug infusion at 1, 3, 5, 7, 10, 15, 20, 30, 45, 60, and 90 min and 2, 3, 4, 5, and 6 h following termination of the infusion. The results of the rate of decrease of drug concentration and the recovery of minute ventilation have been reported elsewhere.¹⁵ All blood samples were immediately processed and subsequently analyzed by a previously validated gas chromatography-mass spectrometry procedure for whole-blood remifentanyl¹⁶ and alfentanil concentrations.¹⁷ The lower and upper limits for the assay were 0.1 ng/ml and 10 ng/ml, respectively, for remifentanyl and 1 ng/ml and 100 ng/ml, respectively, for alfentanil. The interday coefficient of variation for quality-control samples analyzed with the subject samples ranged from 2.7% to 11.5% for remifentanyl and 0% to 13.2% for alfentanil.

Determination of Potency

The average absolute depression of MV and percentage depression of MV at each time interval produced by each drug was calculated and compared using repeated-measures analysis of variance, both within and between groups. A *p* value of .05 was considered significant. The average whole blood concentration of remifentanyl and alfentanil at each of the time points that an MV was measured was also determined. A within-group repeated-measures analysis of variance was performed to confirm that stable concentrations of both opioids were maintained.

Pharmacokinetic and dynamic modeling of opioid concentration to depression of minute ventilation was also performed using an inhibitory sigmoid E_{\max} model:¹⁸

$$E_{(t)} = E_0 - E_{\max} \cdot C_e(t)^\gamma / [EC_{50}^\gamma + C_e(t)^\gamma]$$

where $E_{(t)}$ is the predicted effect of the opioid (minute ventilation during a 5-min hyperbaric challenge) at time *t*; E_0 is the baseline minute ventilation in absence of drug; E_{\max} is the maximum effect of the opioid and would-be apnea (*i.e.*, minute ventilation = 0), and thus, E_{\max} equals the difference between the baseline value E_0 and 0 and therefore was constrained to equal E_0 ; EC_{50} is the opioid concentration that produces 50% of the maximal decrease in minute ventilation; γ is a dimensionless number reflecting the steepness of the curve (the iterative procedure could not find a reasonable solution when γ was estimated; therefore, a reduced model with γ constrained to 1 was used); and C_e is the observed blood concentration at time *t*. We used two procedures to estimate the other parameters in the model. The first procedure used the average baseline value of minute

ventilation for E_0 . The second procedure estimated E_0 along with EC_{50} in the model. Results were similar for both procedures with the exception that in two volunteers the second method failed to converge, compared with the first method, which only failed to converge in one volunteer. We thus used the estimated parameters from the first method. A temporal dissociation between changes in alfentanil and remifentanyl concentration and effect occurs during the onset and offset of drug effect. As this would underestimate EC_{50} if data from postinfusion measurements were used, only the data collected during pseudo-steady state, in which blood concentration and the effect site had equilibrated, were used in this analysis. From this model a concentration-effect curve was generated, and the effect concentration for a 50% depression of minute ventilation was determined for both drugs.

The potency ratio with 95% confidence interval (95% fiducial limits calculated by Fieller's theorem) of remifentanyl to alfentanil was determined from both the concentrations required to titrate the volunteers to an equivalent percent and depression of MV at pseudo-steady state and from the calculated EC_{50} for both drugs. As alfentanil is usually measured as a plasma concentration, it was thus necessary to use a correction for the partitioning of alfentanil between whole blood and plasma, which is 0.63.¹⁹

Results

Eight of the 30 subjects did not complete the entire study (four from each drug group). Six of these subjects (two receiving remifentanyl, four alfentanil) were withdrawn from the study because their MV values were not within the 40-70% depression range from baseline within the prescribed 60 min, despite two adjustments in target concentration. The percent change in MV was < 40% in one subject receiving remifentanyl (38%) and in three subjects receiving alfentanil (37%, 37%, and 29%). The percentage change in MV was > 70% in one subject receiving remifentanyl (79%) and in one subject receiving alfentanil (73%). The other two subjects (remifentanyl group) did not complete the study because of computer-assisted continuous infusion failure. The remaining volunteers consisted of 22 (11 per group) males with American Society of Anesthesiologists physical status I, ranging in age from 19 to 35 yr (mean 25.4 ± 4.6) and weighing from 66.4 to 93.4 kg (mean 77.5 ± 8.0). All volunteers were included in the phar-

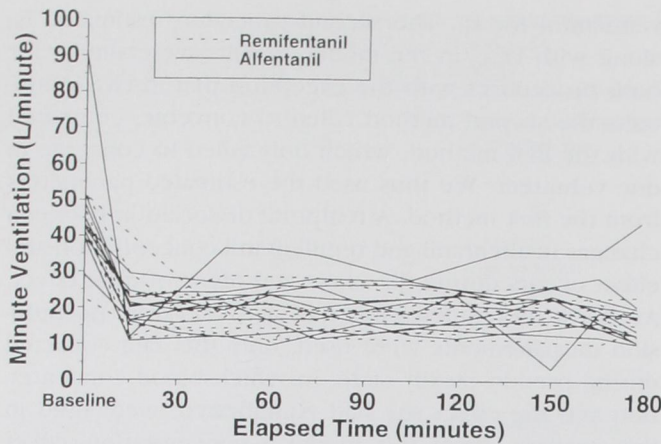


Fig. 2. Decrease in minute ventilation for each subject versus time following the infusion of alfentanil (solid line) and remifentanyl (dashed line) when breathing 7.5% CO₂.

macokinetic/dynamic analysis even if they did not complete the study. In one patient, there were insufficient blood samples to perform the analysis. Thus, the pharmacokinetic and dynamic analysis was performed in 29 of the 30 volunteers who entered the study. In one patient receiving alfentanil, the model did not converge. The recovery of ventilatory function as measured by the context-sensitive half-times has been reported previously.¹⁵

Potency

The individual MVs obtained during the infusion are plotted in figure 2. The changes in arterial carbon dioxide tension are represented in figure 3. Changes in oxygen tension, pH, and end-tidal CO₂ were very similar between the groups. As expected, the baseline MV was statistically different from the MV obtained during drug infusion (average decrease of 55%), but there was no difference within and between groups during the infusion if the baseline values were excluded. The average whole-blood concentration (mean and 95% confidence interval) of remifentanyl required to maintain subjects at between 40 and 70% depression of minute ventilation was 1.2 (0.95–1.45) ng/ml; for alfentanil it was 45.8 (35.2–56.4) ng/ml. This implies that remifentanyl is 39 (26.3–52.1) times more potent than alfentanil, based on whole-blood concentration. The derivation of potency has an uncertainty because of the individual variability.

The concentration–response relationship between remifentanyl and alfentanil whole-blood concentrations and percentage depression in MV for each volunteer is plotted in figure 4. The calculated whole-blood concentration of remifentanyl (mean and 95% confidence inter-

val) necessary to produce a 50% depression in minute ventilation during a 7.5% CO₂ change was 1.17 (0.85–1.49) ng/ml. The EC₅₀ for alfentanil was 49.4 (32.4–66.5) ng/ml. Using this analysis, remifentanyl is 42 (26.0–65.2) times more potent than alfentanil based on whole-blood concentration or 67 (41.3–103.5) times more potent based on alfentanil plasma concentration.

Discussion

In this study we demonstrated that when ventilatory depression is used as a measure of opioid effect, remifentanyl is approximately 40 times more potent than alfentanil (based on their whole-blood concentrations), with a 95% confidence interval of 26–65.

When developing potent drugs such as opioids, it is critical that their pharmacological profiles be described relative to drugs within the same class. To do this the potency of the drug under development relative to its comparators must be established. Ideally potency is determined according to the primary effect of the drug (*i.e.*, for opioids their analgesic efficacy). Pain and pain relief are very subjective measures. Numerous human laboratory models have been proposed to test for analgesic efficacy. The adequacy of many of these models was questioned many years ago by Beecher.⁷ Since then, tooth-pulp stimulation,²⁰ the ischemic tourniquet test,^{21,22} the spring-loaded rod,⁴ and the H reflex²³ have been proposed as models for the measurement of the efficacy of potent analgesics. These models have provided adequate results following single-dose administra-

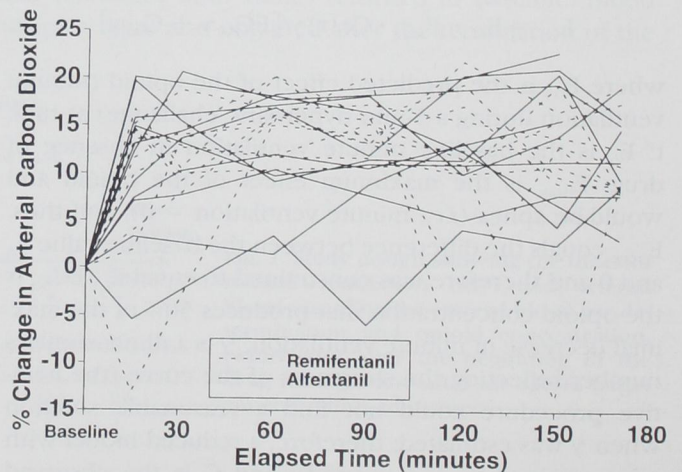


Fig. 3. Percentage changes in arterial carbon dioxide tension for each subject versus time following the infusion of alfentanil (solid line) and remifentanyl (dashed line) when breathing 7.5% CO₂.

Change in minute ventilation with increasing opiate concentration

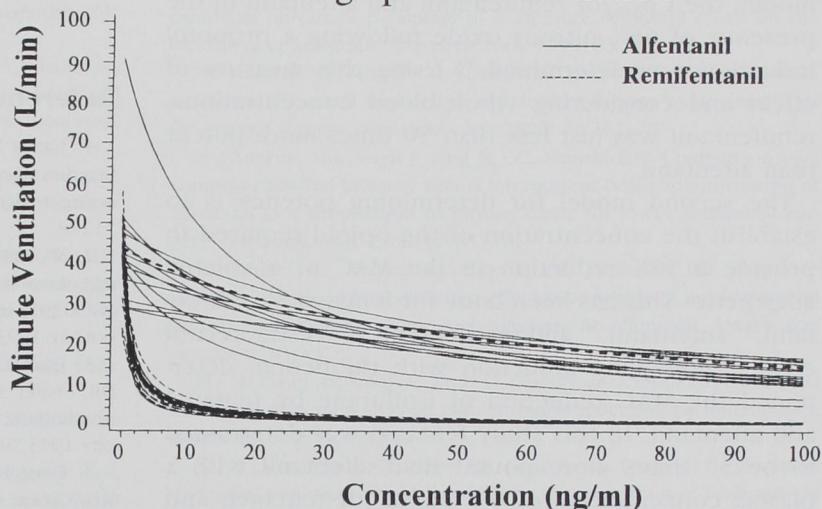


Fig. 4. Relationship between whole-blood concentration of remifentanil (dashed line) and alfentanil (solid line) and percentage depression of minute ventilation using an inhibitory E_{max} model (see text) in each individual. The median response for the remifentanil group is the bold solid line and for the alfentanil group the bold dashed line.

tion of an analgesic but have either not been tested or, by design, are not suitable for evaluating analgesic efficacy during conditions of a continuous infusion. Remifentanil's pharmacokinetic parameters result in an evanescent effect following a single bolus, and thus remifentanil most commonly will be given by continuous infusion. As a result, present laboratory models of analgesic efficacy are likely to be unsuitable in determining the potency of remifentanil during an infusion.

Other models for the assessment of analgesic efficacy are the use of patient-controlled analgesia in postoperative pain models or similar techniques in patients with cancer pain. These models have numerous drawbacks. Drug development must be further along, patients' perceptions of pain are highly variable, and their requests for analgesic drugs *via* a patient-controlled analgesic device are determined by several factors other than pain alone.²⁴ As a result of this marked variability (up to 10-fold for drug concentration), very large numbers of patients are required for such studies.²⁵

To compensate for this, surrogate measures of drug effect have been sought to determine the potency ratio of opioids. Recently, three models have been proposed to measure the relative potency of mu-specific opioid agonists. Several studies have demonstrated the ability of opioids to suppress the electroencephalogram (EEG).^{11,14,19,26} In particular, they have measured simultaneously the suppression of the spectral edge and drug concentration following a brief infusion. From this, the

concentration of the drug necessary to provide a 50% decrease in the spectral edge frequency (EC_{50}) is derived. The EC_{50} concentrations for different opioids are thus assumed to be equipotent. The relationship between the EEG spectral edge frequency and analgesia has not been rigidly determined. In addition, the values of EC_{50} for opioids so far tested are far in excess of the normal therapeutic ranges of these drugs to provide analgesia. The concentration that produces a 50% decrease in the spectral edge of the EEG is much closer to the concentration of the opioid that provides loss of consciousness than to its analgesic concentration. The relative potency of known opioids determined by this model has, however, correlated well with other measures of opioid potency.⁸ Using this model in a crossover study with volunteers, Egan *et al.*¹⁹ determined the potency of remifentanil to alfentanil as approximately 20 to 1 based on whole blood concentrations. Another EEG-derived parameter, the canonical univariate parameter, has been shown to be a better measure of opioid effect on EEG than the spectral edge. Using this parameter, Gambus *et al.*²⁷ found a potency ratio of remifentanil to alfentanil of 45:1 based on plasma alfentanil concentration (thus, of 30:1 if corrected to whole-blood concentration).

The two other models for determining opioid potency have utilized the response to skin incision as their measure of effect. Ausems *et al.*^{28,29} determined the plasma concentration of the drug that is in equilibrium with its biophase that will prevent movement

at skin incision in 50% of patients (Cp_{50}) of alfentanil in the presence of 66% nitrous oxide. Using a similar model, the Cp_{50} for remifentanil and alfentanil in the presence of 66% nitrous oxide following a propofol induction was determined.³⁰ Using this measure of effect and considering whole-blood concentrations, remifentanil was just less than 50 times more potent than alfentanil.

The second model for determining potency is to establish the concentration of the opioid required to provide a 50% reduction in the MAC of a volatile anesthetic. This has been done for fentanyl,^{31,32} alfentanil,³² sufentanil,³³ and remifentanil.³⁴ Westmoreland *et al.*,³² following induction with thiopental, determined the MAC reduction of isoflurane by fentanyl and alfentanil. In this study fentanyl was determined to be 57 times more potent than alfentanil with a plasma concentration of 0.5 ng/ml for fentanyl, and 28.8 ng/ml for alfentanil producing a 50% reduction in the MAC of isoflurane. Using the same methodology (without thiopental), a remifentanil whole-blood concentration of 1.37 ng/ml,³⁴ a fentanyl plasma concentration of 1.7 ng/ml,³¹ and a sufentanil plasma concentration of 0.145 ng/ml³³ produced a 50% reduction in the MAC of isoflurane. Based on these values for a 50% MAC reduction of isoflurane, and adjusting for the absence of thiopental, equivalent concentrations of the opioids are fentanyl (plasma) 1 ng/ml, sufentanil (plasma) 0.08 ng/ml, alfentanil (plasma) 57 ng/ml, and remifentanil (whole blood) 0.82 ng/ml. Converting alfentanil plasma concentration to a whole-blood concentration would make remifentanil whole-blood concentration 36 times more potent than alfentanil whole-blood concentration. This value lies between the potency determined for remifentanil using ventilatory response to 7.5% CO_2 and that determined from the decrease in spectral edge frequency as the measure of effect. Moreover, because of the interindividual variability, the Cp_{50} and the derived potency ratio have degrees of uncertainty, and most of these values lie within the 95% confidence interval of the ratio determined within the present study.

In conclusion, using depression of minute ventilation to 7.5% CO_2 , we determined (based on whole-blood concentration in equilibration with its effect site) that remifentanil is approximately 40 times more potent than alfentanil. Studies comparing the efficacy of remifentanil to other opioids should incorporate the difference in potency established by this study.

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