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Remifentanil Versus Alfentanil

Comparative Pharmacokinetics and Pharmacodynamics in Healthy Adult Male Volunteers

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Background: Remifentanil is an esterase-metabolized opioid with a rapid clearance. The aim of this study was to contrast the pharmacokinetics and pharmacodynamics of remifentanil and alfentanil in healthy, adult male volunteers.

Methods: Ten volunteers received infusions of remifentanil and alfentanil on separate study sessions using a randomized, open-label crossover design. Arterial blood samples were analyzed to determine drug blood concentrations. The electroencephalogram was employed as the measure of drug effect. The pharmacokinetics were characterized using a moment analysis, a nonlinear mixed effects model (NONMEM) population analysis, and context-sensitive half-time computer simulations. After processing the raw electroencephalogram to obtain the spectral edge parameter, the pharmacodynamics were characterized using an effect compartment, inhibitory maximum effect model.

Results: Pharmacokinetically, the two drugs are similar in terms of steady-state distribution volume (VD_{ss}), but remifentanil's central clearance (CL_c) is substantially greater. The

NONMEM analysis population pharmacokinetic parameters for remifentanil include a CL_c of $2.9 \text{ l} \cdot \text{min}^{-1}$, a VD_{ss} of 21.81, and a terminal half-life of 35.1 min. Corresponding NONMEM parameters for alfentanil are $0.361 \text{ l} \cdot \text{min}^{-1}$, 34.11, and 94.5 min. Pharmacodynamically, the drugs are similar in terms of the time required for equilibration between blood and the effect-site concentrations, as evidenced by a $T_{1/2,ke_0}$ for remifentanil of 1.6 min and 0.96 min for alfentanil. However, remifentanil is 19 times more potent than alfentanil, with an effective concentration for 50% maximal effect of $19.9 \text{ ng} \cdot \text{ml}^{-1}$ versus $375.9 \text{ ng} \cdot \text{ml}^{-1}$ for alfentanil.

Conclusions: Compared to alfentanil, the high clearance of remifentanil, combined with its small steady-state distribution volume, results in a rapid decline in blood concentration after termination of an infusion. With the exception of remifentanil's nearly 20-times greater potency (30-times if alfentanil partitioning between whole blood and plasma is considered), the drugs are pharmacodynamically similar. (Key words: Analgesics, opioids: alfentanil; GI87084B; remifentanil. Pharmacokinetics: alfentanil; computer simulations; context-sensitive half-times; GI87084B; population modeling; remifentanil. Pharmacodynamics: alfentanil; computer simulations; electroencephalography; GI87084B; population modeling; remifentanil.)

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REMIFENTANIL (hydrochloride salt of 3-[4-methoxy-carbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester), formerly known as GI87084B, is a synthetic opioid that exhibits classic μ -agonist pharmacologic effects.¹ Although chemically related to the fentanyl family of short-acting 4-anilidopiperidine derivatives commonly used as supplements to general anesthesia, remifentanil is structurally unique among currently available opioids because of its ester linkages. As an ester, remifentanil is susceptible to hydrolysis by blood and tissue nonspecific esterases, resulting in rapid metabolism to essentially inactive compounds. Preliminary evidence from volunteer and patient studies suggests that remifentanil may constitute the first true ultrashort-acting opioid for use as a supplement to general anesthesia.²⁻⁴ The aim of this study was to contrast the clinical pharmacology of remifen-

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tanil and alfentanil in healthy, adult male volunteers by constructing a detailed pharmacokinetic/pharmacodynamic model for each drug using an open-label, randomized, crossover study design.

Materials and Methods

Recruitment, Instrumentation, and Safety Monitoring

After obtaining Institutional Review Board approval and informed consent, ten American Society of Anesthesiology (ASA) physical status 1 volunteers were enrolled in the study. Only English-speaking men between the ages of 18–40 yr without history of significant medical illness or medication requirements who were within 15% of their ideal body weight were eligible for participation. Prospective volunteers were ineligible if they had a history of alcohol abuse or illegal drug use, a habit of tobacco use greater than 10 cigarettes per day, a history of hypersensitivity to opioids, or a record of significant psychiatric disease. To confirm eligibility, each subject underwent a physical examination and a comprehensive battery of laboratory tests, including serum chemistries, liver and renal function tests, a complete blood count, a urinalysis, a urine drug screen, and an electrocardiogram.

Each subject was brought to the study site without premedication. An 18-G catheter was placed in a forearm vein for drug and fluid administration. A 20-G radial artery catheter was placed for blood sampling and continuous blood pressure monitoring. A solution of normal saline was infused intravenously at an approximate rate of 60 ml/h. Safety monitors included a continuous five-lead electrocardiogram, continuous pulse oximetry, and a precordial stethoscope.

Instrumentation for electroencephalographic (EEG) monitoring was performed in accordance with the International 10–20 system.⁵ Four channels (F_3-P_3 , F_4-P_4 , C_3-P_3 , C_4-P_4) of the EEG were amplified and recorded using a Nihon Kohden EEG machine (model 5210, Nihon Kohden, Irvine, CA).

After the instrumentation was completed, the volunteers received 0.2 mg glycopyrrolate intravenously to prevent opioid-induced bradycardia and 0.5 mg pancuronium intravenously to mitigate opioid-induced muscle rigidity. Volunteers breathed 100% O₂ by face mask delivered *via* a nonbreathing circuit in preparation for drug administration.

Volunteers were randomized to receive either remifentanil or alfentanil during their initial visit and the

other drug on their subsequent visit. Study sessions were separated by at least 2 weeks but no longer than 4 weeks. Both remifentanil and alfentanil were administered intravenously as a constant rate infusion by a laboratory syringe pump (Harvard Apparatus XG2000, South Natick, MA) for at least 10 min or until maximal changes were evident on the raw EEG. Remifentanil was administered at $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (except the first subject, who received $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and alfentanil was administered at $1,500 \mu\text{g} \cdot \text{min}^{-1}$.

During both visits, 3-ml arterial blood samples were obtained at preset intervals, with more rapid sampling during the infusion and immediately after termination of the infusion. After the infusion commenced, samples were collected every 30 s from 1 to 5 min, every minute from 6 to 10 min, and every 2 min from 12 to 20 min until the infusion was terminated. After the infusion was stopped, samples were collected every 30 s from 1 to 5 min, every minute from 6 to 10 min, and every 2 min from 12 to 20 min. Thereafter, samples were obtained at 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 120, 150, 180, 210, and 240 min after the infusion was stopped. Additional samples at 360, 480, and 600 min after infusion were obtained during the alfentanil sessions.

During drug infusion, ventilation was assisted by bag and mask with 100% O₂ as needed. A continuous infusion of succinylcholine was used as necessary to mitigate the effects of opioid-induced rigidity and to facilitate ventilation. Frequent arterial blood gas analysis confirmed the adequacy of ventilation and oxygenation.

Vital signs and subjective well-being were monitored after the end of the infusion for at least 3 h. Adverse events associated with drug administration were recorded as they occurred. Nausea and/or vomiting were treated as necessary by an intravenous injection of 10 mg metoclopramide.

Blood Sample Processing and Concentration Assay

Because of remifentanil's metabolic pathway, special processing was necessary to prevent continued metabolism of remifentanil after sample collection. The details of our sample-processing technique have been described previously.² Both the remifentanil and alfentanil samples were processed in this manner.

Remifentanil blood concentrations were measured by a high-resolution, gas chromatographic, mass spectrometry assay with a quantitation limit of $0.1 \text{ ng} \cdot \text{ml}^{-1}$.

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Study sessions no longer than 1 h were administered infusion by a pump until maximal. Remifentanil except the first $1\text{ ng}\cdot\text{ml}^{-1}$, and alfentanil $1\text{ ng}\cdot\text{ml}^{-1}$. Samples were rapid sampling after termination of infusions, samples every minute for 12 to 20 min after the infusion every 30 s from 1 min, and every 10 s samples were taken at 0, 70, 80, 90, 100 min after the infusion at 360, 480, and 600 s during the

assisted by A continuous was necessary to rigidity and to arterial blood gas ventilation and

were monitored for 3 h. Adverse reactions were reported vomiting after injection of 10 mg.

concentration pathway, special continued metabolism. The drugs have been determined and alfentanil manner. measured by mass spectrometry of $0.1\text{ ng}\cdot\text{ml}^{-1}$

and an interassay coefficient of variation of less than 15% for concentrations greater than $0.1\text{ ng}\cdot\text{ml}^{-1}$. Tetradeuterated remifentanil was included in the collection tubes as an internal standard to correct for variations in recovery among samples.⁶

Alfentanil blood concentrations were determined by a gas chromatographic, mass spectrometry technique with an interassay coefficient of variation of less than 10% and a quantitation limit of $1\text{ ng}\cdot\text{ml}^{-1}$.⁷ Fentanyl was included as an internal standard.

EEG Signal Processing

The digitized raw EEG data were processed by computer to obtain the spectral edge parameter, a univariate summary descriptor identifying the frequency below which 95% of the EEG power is located.⁸ After filtering with a 50-Hz low-pass filter, the raw signal was analyzed in epochs of 2 s by Fourier transformation to separate it into frequency bins between 0.5 and 30 Hz. The power spectrum was calculated by squaring the amplitudes of the individual frequency components. Finally, the spectral edge was determined by calculating the area under the power *versus* frequency histogram and identifying the frequency below which 95% of the total area is found.

Pharmacokinetic Analysis

The pharmacokinetics were analyzed using three techniques. A classic moment analysis (area under the curve analysis) was done to facilitate comparison of each drug's model independent parameters in the same individual. A mixed-effect population approach based on the computer program NONMEM# was completed to estimate the population compartmental pharmacokinetic parameters. Finally, to address the clinical aspects of the mathematically based pharmacokinetic analysis, computer simulations of the context-sensitive half-times based on the NONMEM population pharmacokinetic parameters were performed.

Moment Analysis. Applying the theory of statistical moments to pharmacokinetics,⁹ a model independent moment analysis was performed to calculate the clearance (CL), mean residence time (MRT), and apparent volume of distribution at steady-state (VD_{ss}) for both drugs in each subject. The area under the concentration *versus* time curve (AUC) was calculated for each blood

concentration (C_b) *versus* time (t) plot using the trapezoidal method with linear interpolation when concentrations were increasing and log-linear interpolation when concentrations were decreasing.¹⁰ The terminal slope for each data set was estimated by log-linear regression after visually identifying the terminal portion of each curve.

CL, MRT, and VD_{ss} were calculated using standard equations. Individual moment analysis parameters for both drugs in each subject were contrasted in graph form.

Nonlinear Mixed Effects Model Compartmental Analysis. The population compartmental pharmacokinetic parameters for both drugs were estimated using the NONMEM approach. Because it had been previously demonstrated for the remifentanil dose range studied, linear pharmacokinetics was assumed for the purposes of this analysis.^{2,3} In contrast with the two-stage approach, wherein the population pharmacokinetic model is obtained by averaging the parameters estimated from individuals, NONMEM simultaneously analyzes an entire population's data and provides estimates of typical values for the pharmacokinetic parameters with an estimate of the parameter's interindividual variability within the population studied.

A three-compartment mamillary model was fit to the remifentanil and alfentanil concentration *versus* time data. Interindividual error on each parameter was modeled using a log-normal error model:

$$\theta_{\text{individual}} = \theta_{\text{typical}} e^{\eta_{\text{individual}}},$$

where $\theta_{\text{individual}}$ is the true value in the individual, θ_{typical} is the population mean estimate, and $\eta_{\text{individual}}$ is a random variable whose distribution is estimated by NONMEM with a mean of zero and a variance of ω^2 . Residual error was modeled assuming a log-normal distribution.

After obtaining estimates for the population volumes and clearances from NONMEM, the other three-compartment mamillary model parameters (micro and macro rate constants) were calculated using standard equations.¹¹

The performance of the population models constructed by NONMEM for both drugs was assessed in terms of the ability to predict the measured blood concentrations. The models were quantitatively assessed in terms of weighted residuals (WRs), the difference between a measured blood concentration (C_m) and the model-predicted concentration (C_p) in terms of C_p . Thus, WR can be defined as:

Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California, San Francisco, 1979.

$$WR = \frac{C_m - C_p}{C_p}$$

Using this definition, the WRs for the NONMEM population models were computed at every measured data point. Using the WR data, the overall inaccuracy of the model was determined by computing the median absolute weighted residual (MDAWR), defined as:

$$MDAWR = \text{median}\{|WR_1|, |WR_2|, \dots, |WR_n|\},$$

where n is the total number of samples in the study population. Using this formula, the MDAWRs for the population models constructed by NONMEM were computed for each drug.

The performance of the models was visually assessed by plotting the C_m/C_p versus time and examining the plots for accuracy and bias.

Computer Simulations. Computer simulations using the pharmacokinetic parameters obtained from the NONMEM compartmental analysis were performed to provide an illustration of the predicted decline in blood concentrations when remifentanil and alfentanil are administered by infusion. These simulations predict the time necessary to achieve a 50% or 80% decrease in drug concentration in the blood after termination of a variable-length infusion targeted to a constant drug concentration. The simulations are based on Euler's solution to the three-compartment model with a step size of 1 s.

Pharmacodynamic Analysis

The pharmacodynamics were described using an effect compartment model in which k_{eo} , a first-order elimination rate constant characterizing effect-site equivalent, is used to estimate the apparent effect-site concentrations.¹² The pharmacodynamic analysis proceeded in three steps for each data set. First, k_{eo} was estimated using a hysteresis loop minimization technique. Second, the apparent concentration-effect relationship resulting from the hysteresis loop minimization technique was parametrically modeled assuming a sigmoidal shape for the relationship. Finally, making use of the k_{eo} and other pharmacokinetic and pharmacodynamic parameters estimated from the study, computer simulations were performed to contrast the onset, magnitude, and duration of effect resulting from equipotent doses of remifentanil and alfentanil.

K_{eo} Estimation Procedure. K_{eo} was estimated using a hysteresis loop minimization technique.¹³ The theoretical foundation of this technique is that, in the effect

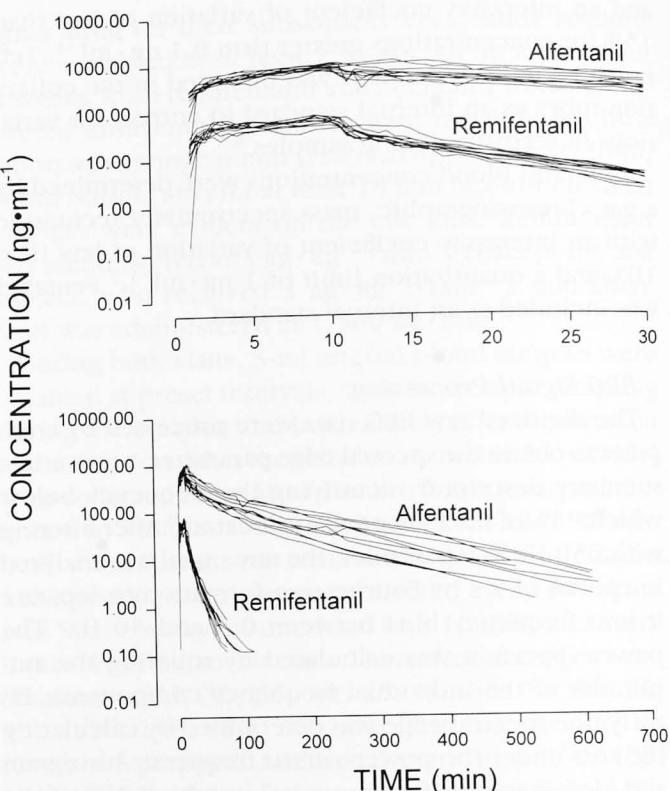


Fig. 1. The raw concentration *versus* time data. Each line represents one volunteer. The vertical axis, representing remifentanil and alfentanil concentrations, is plotted on a log scale. The upper panel depicts the first 30 min only, whereas the lower panel shows the entire concentration *versus* time profile.

site, there should be no delay or hysteresis between changes in drug concentration and changes in pharmacologic effect. In summary, this k_{eo} -estimating technique performs a numeric convolution of the measured drug concentrations with a candidate k_{eo} value to calculate the apparent effect-site concentrations. The optimal k_{eo} value minimizes the area of the hysteresis loop formed by plotting the apparent effect-site concentration *versus* effect. Potential k_{eo} values are sequentially tested until the optimal estimate of k_{eo} is obtained. The algorithm is thus an iterative process in which the hysteresis loops determined by numeric convolution of the measured drug concentrations with a potential k_{eo} are successively "collapsed" until a k_{eo} that results in minimal hysteresis is found. The optimal k_{eo} is used to calculate the apparent effect-site concentrations and thus identify the "pseudosteady-state" concentration-effect relationship.

Parametric Modeling of the Concentration-Effect Relationship. Because plots of the concentra

Table 1. Moment Ana

Subject No.	
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Mean	
SD	

CL = clearance; ERT =

effect relationship were sigmoid in equation (12). H relationship par squares nonlinear spreadsheets (Mic

where E is the p level, E_{max} is ma tration, γ is a m the effect-site α maximal effect, c concentration dynamic parameter a predicted effe remifentanil and

Computer Sim performed using dynamic model application of tulation, intended, was a sim tanil and alfenta potent doses alfentanil). The rate magnitude of effect-site co puter-controlled University, Palo both remifentan

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Table 1. Moment Analysis Pharmacokinetic Parameters

Subject No.	CL (l · min ⁻¹)		MRT (min)		VD _{ss} (l)	
	REMI	ALF	REMI	ALF	REMI	ALF
1	3.5	0.35	8.4	120.3	29.3	41.6
2	2.5	0.28	9.0	127.4	22.4	35.9
3	2.8	0.50	5.4	66.5	15.2	33.1
4	3.4	0.53	7.3	89.7	25.1	47.5
5	3.2	0.37	6.5	97.7	20.5	36.5
6	3.2	0.45	10.8	81.6	34.3	36.9
7	3.5	0.40	6.2	121.2	21.8	48.2
8	2.5	0.32	8.7	93.5	21.9	29.8
9	3.3	0.40	8.9	131.5	29.5	52.4
10	2.4	0.24	8.6	129.9	20.9	31.0
Mean	3.0	0.38	8.0	105.9	24.1	39.3
SD	0.4	0.09	1.6	23.0	5.5	7.8

CL = clearance; MRT = mean residence time; VD_{ss} = volume of distribution at steady state; REMI = remifentanil; ALF = alfentanil; SD = standard deviation.

effect relationship determined by the estimation of k_{e0} were sigmoid in shape, an inhibitory "sigmoid E_{max}" equation (*i.e.*, Hill equation) was used to model the relationship parametrically.¹⁴ Using extended least-squares nonlinear regression implemented on an Excel spreadsheet (Microsoft, Redmond, WA), the equation:

$$E = E_0 - \frac{E_{\max} \cdot C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}},$$

where E is the predicted effect, E₀ is the baseline effect level, E_{max} is maximal effect, C_e is effect-site concentration, γ is a measure of curve steepness, and EC₅₀ is the effect-site concentration that produces 50% of maximal effect, was fit to the effect *versus* effect-site concentration data. Having estimated the pharmacodynamic parameters, the model was used to calculate a predicted effect at each measured concentration of remifentanil and alfentanil.

Computer Simulations. Computer simulations were performed using the full pharmacokinetic/pharmacodynamic model from the study to illustrate the clinical application of the estimated parameters. The first simulation, intended to illustrate time to peak concentration, was a simulation of effect-site levels of remifentanil and alfentanil after bolus administration of equi-potent doses (185 µg remifentanil, 3,500 µg alfentanil). The second simulation, intended to illustrate magnitude and duration of effect, was a simulation of effect-site concentrations that result from a 2-h computer-controlled infusion using Stanpump (Stanford University, Palo Alto, CA) targeted to an EC₅₀ level for both remifentanil and alfentanil.

Results

Recruitment, Instrumentation, and Safety Monitoring

All ten volunteers originally enrolled completed the study. The volunteers were comparable in terms of age, lean body mass, and ASA physical status. Demographic means included an age of 28.5 ± 4.8 yr, weight of 83.5 ± 11.2 kg, and height of 183.7 ± 5.8 cm (\pm SD).

All subjects received at least a 10-min infusion of remifentanil and alfentanil. One remifentanil subject required 14 min to exhibit maximal EEG changes, whereas two alfentanil subjects required infusions of 16 and 14 min, respectively, to reach maximal EEG changes. No infusion was terminated early because of an adverse event.

With the exception of adverse events such as muscular rigidity and nausea/vomiting that were anticipated as part of this protocol, no significant or unexpected complications were associated with remifentanil or alfentanil administration. In particular, there were no untoward hemodynamic events such as severe bradycardia, tachycardia, or hypotension requiring therapy or termination of the infusion. One subject experienced a brief (31 s) period of asymptomatic supraventricular tachycardia during remifentanil administration that spontaneously resolved.

Pharmacokinetic Analysis

The infusion schemes applied in this protocol resulted in concentration *versus* time curves character-

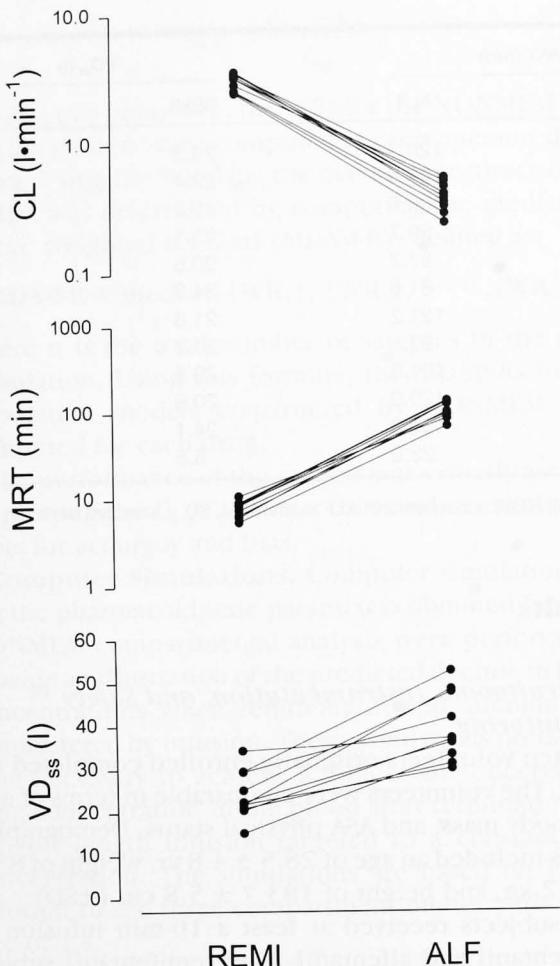


Fig. 2. The clearance (CL), mean residence time (MRT), and volume of distribution at steady-state (VD_{ss}) of remifentanil (REMI) versus alfentanil (ALF) as determined by moment analysis. CL is expressed in liters per minute, MRT in minutes, and VD_{ss} in liters. Each line connects the solid circles representing these remifentanil and alfentanil parameters in the same subject. The vertical axis for the CL and MRT panels is plotted on a log scale.

istic of brief intravenous infusions. The raw data plots for each drug are contrasted in figure 1.

Moment Analysis. The moment analysis reveals substantial differences in the pharmacokinetics of remifentanil and alfentanil. Remifentanil CL is approximately 8 times greater than alfentanil's. Similarly, remifentanil's MRT is roughly 13-fold shorter than alfentanil's. With respect to distribution, the drugs are more alike. Alfentanil's VD_{ss} is approximately 1.6 times greater than remifentanil's.

The individual and mean CL, MRT, and VD_{ss} values are shown in table 1. Figure 2 contrasts the model in-

Table 2. NONMEM Three-compartment Population Pharmacokinetic Parameters

Parameter	Remifentanil	Alfentanil
Fractional coefficients		
A	0.85	0.81
B	0.15	0.14
C	0.002	0.05
Hybrid rate constants (min^{-1})		
α	0.7521	0.9480
β	0.1097	0.0426
γ	0.0197	0.0073
Microrate constants (min^{-1})		
k10	0.3847	0.0880
k12	0.2569	0.6161
k13	0.0128	0.0709
k21	0.2066	0.2066
k31	0.0205	0.0163
Half-lives (min)		
α	0.9	0.7
β	6.3	16.3
γ	35.1	94.5
Volumes (L)		
Central	7.6 (0.32)	4.1 (0.33)
Peripheral 1	9.4	12.2
Peripheral 2	4.7	17.8
Steady state	21.8	34.1
Clearances ($\text{L} \cdot \text{min}^{-1}$)		
Central	2.92 (0.12)	0.36 (0.22)
Intercompartmental 1	1.95	2.52
Intercompartmental 2	0.10	0.29

Values in parentheses are coefficient of variation.

dependent parameters for each drug in the same individual.

Nonlinear Mixed Effects Model Compartmental Analysis. As with the moment analysis, the NONMEM compartmental analysis reveals significant contrast between the pharmacokinetic parameters of remifentanil and alfentanil. Remifentanil's steady-state distribution volume is moderately smaller than alfentanil's. Remifentanil's clearance, however, is significantly greater than alfentanil's, a difference that is nearly an order of

Table 3. NONMEM Three-compartment Population Model Weighted Residuals

Residuals	Median (MDAWR)	10th Percentile	90th Percentile
Remifentanil	15.9	3.3	39.9
Alfentanil	13.2	2.6	40.0

MDAWB = median absolute weighted residual

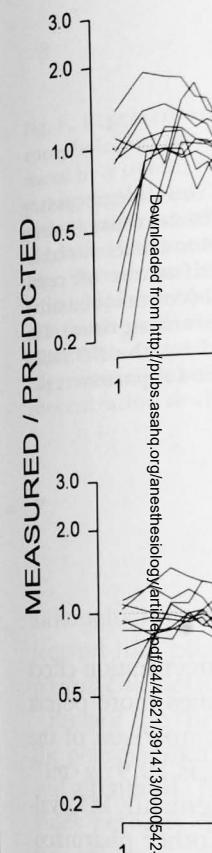


Fig. 3. The residual population models consist as defined in the text. The parameter α represents the percentage applied to an individual. Concentrations were plotted represented by a straight line.

magnitude. The t
for each drug est
are shown in tab

The performance of these NONMEM drugs are represented for compartmental models of approximately 10 hours along with the 10 models in table 3. Figure 1 shows the systematic bias, the first few minutes during the first few minutes at the end of sampling.

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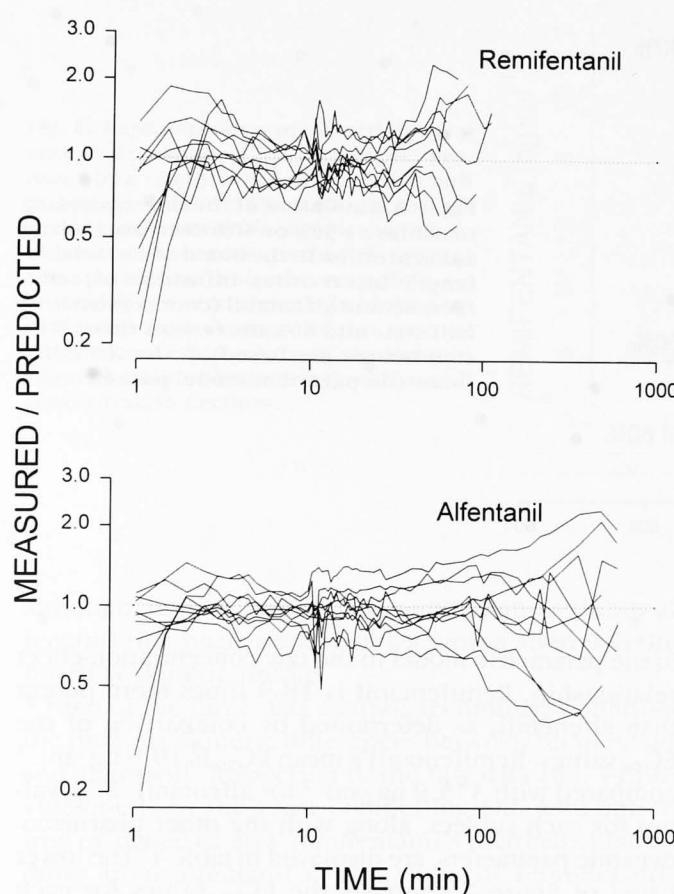


Fig. 3. The residual errors for the three-compartment population models constructed using the NONMEM approach (WR as defined in the text, + 1 to plot on a log scale). Each line represents the performance of the population model when applied to an individual data set. A subject whose blood concentrations were perfectly predicted by the model would be represented by a straight line at 1.

magnitude. The three-compartment model parameters for each drug estimated using the NONMEM approach are shown in table 2.

The performance of the NONMEM models for both drugs are representative of what is generally expected for compartmental population models, with an MDAWR of approximately 15%. The MDAWRs for both models, along with the 10th and 90th percentiles, are shown in table 3. Figure 3 is a plot of the C_m/C_p versus time of these NONMEM models. Although there is no gross systematic bias, the models are obviously less accurate during the first few minutes of the infusion, during the first few minutes after stopping the infusion, and near the end of sampling.

Computer Simulations. The context-sensitive half-time simulations indicate that the decrease in blood

concentration after drug administration is substantially more rapid for remifentanil than for alfentanil. Only 3 min is necessary to achieve a 50% decrease in remifentanil blood drug concentration after termination of an infusion despite lengthy infusions. Similarly, an 80% decrease in remifentanil blood concentration (*i.e.*, 80% decrement time) can be achieved in 11 min. This is in contrast to the simulations for alfentanil; the time to achieve a decrease in blood concentration by 50% or 80% eventually plateaus at 46 and 161 min, respectively, exhibiting a marked dependence on the infusion duration. The results of these computer simulations are depicted in figure 4.

EEG Pharmacodynamic Analysis

Both remifentanil and alfentanil produce EEG changes characteristic of potent μ -receptor agonists. These changes consist of decreasing frequency and increasing amplitude in the raw EEG waveform, culminating eventually in pronounced δ -wave activity at maximal drug effect. An example of raw EEG signal from a remifentanil subject that is representative of the EEG changes observed in all subjects for both drugs is shown in figure 5.

When processed by computer, the profound δ -wave activity produced by both drugs translates into a significant downward shift in the spectral edge parameter of the EEG. Figure 6 shows a typical set of spectral edge parameter *versus* time data from a remifentanil subject.

K_{e0} Estimation. Remifentanil and alfentanil are similar with respect to the time required for equilibration of peak blood concentration and peak effect, as evidenced by their roughly equivalent k_{e0} values. Remifentanil's $T_{1/2}k_{e0}$ is 1.6 min; alfentanil's is 0.96 min. The k_{e0} and $T_{1/2}k_{e0}$ values for each subject are shown in table 4. The upper panel of figure 7 contrasts the $T_{1/2}k_{e0}$ values for each drug in the same subject. Raw and collapsed remifentanil hysteresis loops representative of the entire data set for both drugs are shown in the upper and middle panels of figure 8. Figure 8 illustrates how the k_{e0} -optimizing procedure results in "collapsing" the raw hysteresis loop, thus identifying the pseudosteady-state concentration-effect relationship that then can be subjected to parametric modeling.

Parametric Modeling of the Concentration-Effect Relationship. Except for potency, the parametric modeling fails to reveal any significant differences in the EEG pharmacodynamics of remifentanil and alfentanil. The lower panel of figure 8 depicts a typical fit

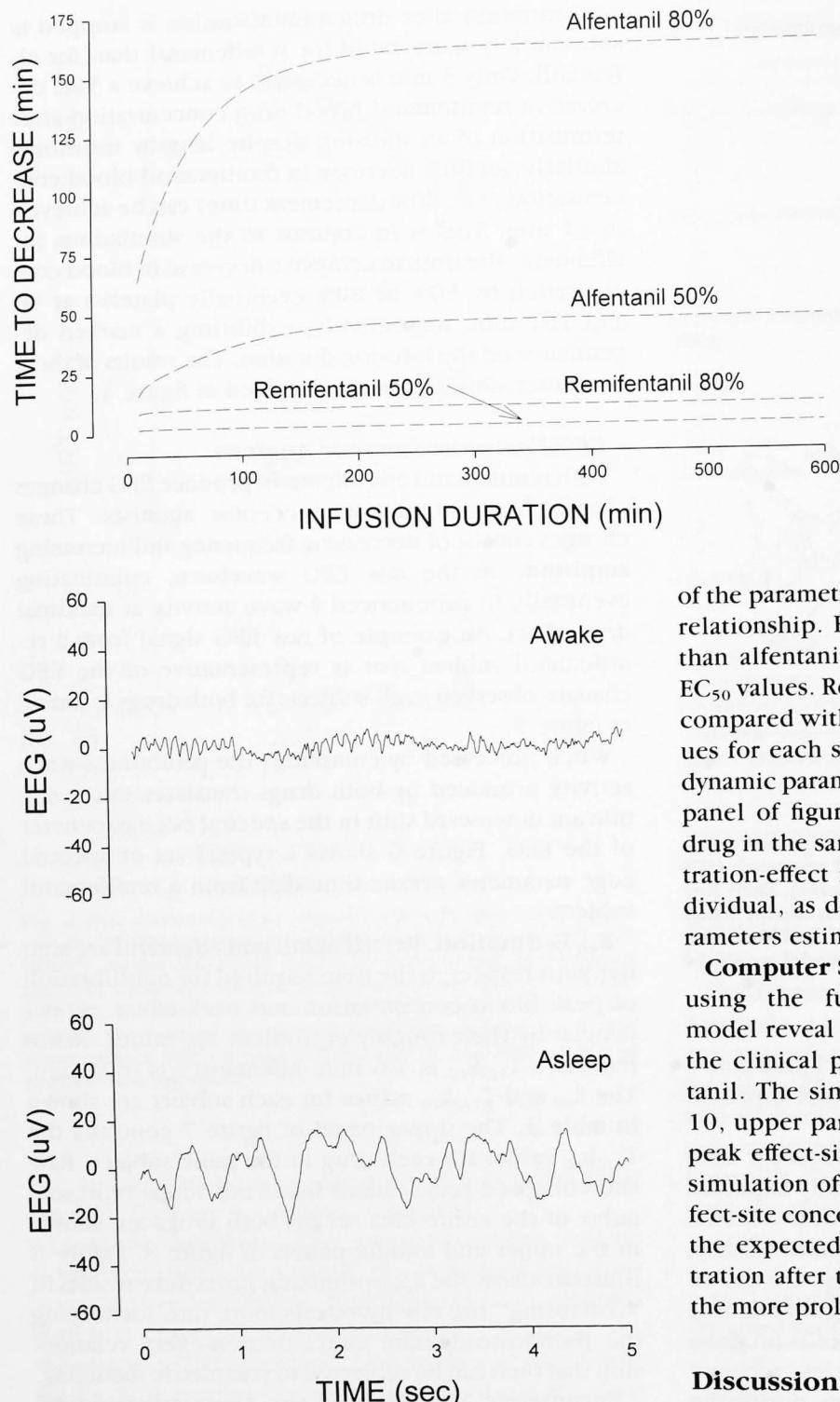


Fig. 4. A simulation of the time necessary to achieve a 50% or 80% decrease in drug concentration in the blood after variable-length intravenous infusions of remifentanil and alfentanil (context-sensitive half-time and 80% decrement time). The simulations are based on the NONMEM three-compartment model parameters.

Fig. 6. Representative encephalographic produced by a 10-min infusion at $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The dotted line represents the edge parameter. No relationship between concentration and change in edge, with a rapid edge to baseline value concentration decline.

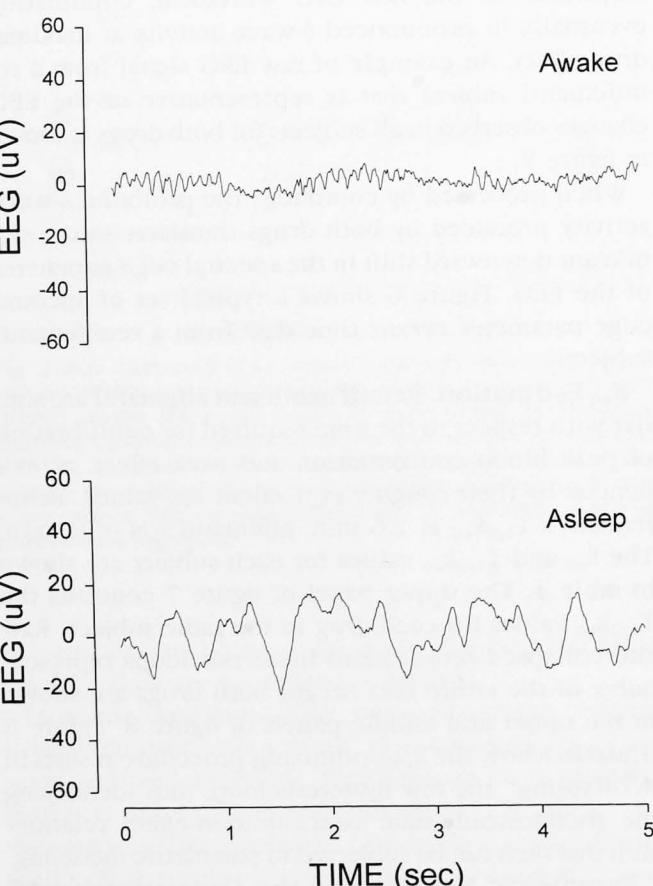


Fig. 5. The raw electroencephalographic (EEG) changes produced by maximal remifentanil effect (asleep) compared to the awake state in a single subject. These changes are representative of the EEG effects observed in all subjects with both remifentanil and alfentanil.

of the parametric model to the raw concentration-effect relationship. Remifentanil is 18.9 times more potent than alfentanil, as determined by comparison of the EC_{50} values. Remifentanil's mean EC_{50} is $19.9 \text{ ng} \cdot \text{ml}^{-1}$ compared with $375.9 \text{ ng} \cdot \text{ml}^{-1}$ for alfentanil. EC_{50} values for each subject, along with the other pharmacodynamic parameters, are displayed in table 4. The lower panel of figure 7 contrasts the EC_{50} values for each drug in the same subject. Figure 9 depicts the concentration-effect relationships for both drugs in each individual, as determined by the pharmacodynamic parameters estimated.

Computer Simulations. The computer simulations using the full pharmacokinetic/pharmacodynamic model reveal important similarities and differences in the clinical pharmacology of remifentanil and alfentanil. The simulation of equipotent bolus doses (fig. 10, upper panel) illustrates a nearly identical time to peak effect-site concentration for the two drugs. The simulation of a 2-h infusion targeted to equivalent effect-site concentrations (fig. 10, lower panel) illustrates the expected rapid decrease in remifentanil concentration after termination of the infusion compared to the more prolonged decline in alfentanil concentration.

Discussion

This study has contrasted the pharmacokinetics and pharmacodynamics of remifentanil and alfentanil in a population of healthy adult male volunteers using a randomized, open-label, crossover design. In summary,

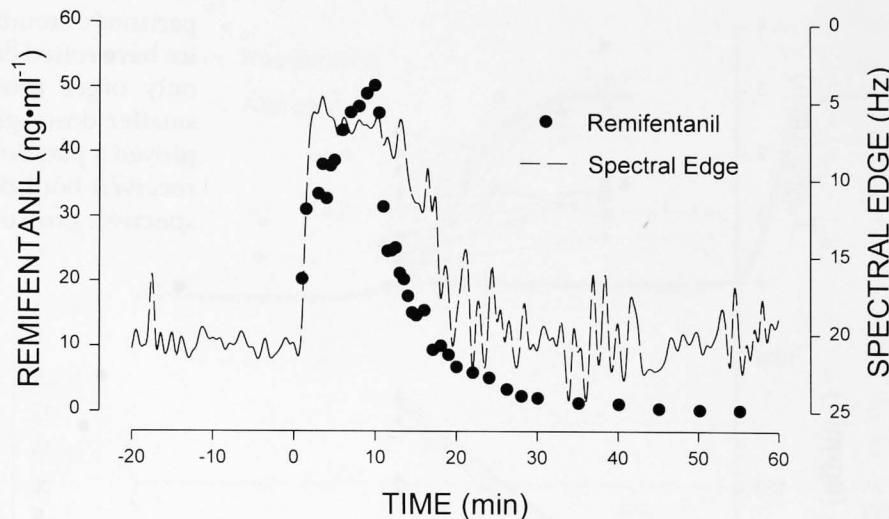
Table 4. Pharmacokinetic Parameters

Subject No.	REMI (ng · kg ⁻¹ · min ⁻¹)	ALF (ng · kg ⁻¹ · min ⁻¹)
1	23.0	375.9
2	18.0	375.9
3	27.0	375.9
4	18.0	375.9
5	19.0	375.9
6	22.0	375.9
7	19.0	375.9
8	11.0	375.9
9	13.0	375.9
10	10.0	375.9
Mean		375.9
SD		375.9

REMI = remifentanil; ALF = alfentanil.

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Fig. 6. Representative processed electroencephalographic (EEG) changes produced by a 10-min infusion of remifentanil at $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The solid circles represent remifentanil blood concentrations; the dotted line represents the EEG spectral edge parameter. Note the very close relationship between changes in blood concentration and changes in the spectral edge, with a rapid return of the spectral edge to baseline values as the remifentanil concentration declines.



although differing in potency, remifentanil exhibits alfentanil-like pharmacodynamics with a shorter-acting pharmacokinetic profile.

Each of the three data analysis techniques confirmed the pharmacokinetic differences between remifentanil and alfentanil. Inspection of the raw data (fig. 1) provides perhaps the most compelling and assumption-free evidence of how remifentanil's pharmacokinetics differ from alfentanil's. The slope of remifentanil's concentration decline after termination of the infusion is markedly steeper than alfentanil's.

Figure 2 illustrates that remifentanil CL is nearly an order of magnitude greater than alfentanil's. This is reflected in the short MRT. With regard to tissue distribution,

the differences are not as marked, with alfentanil's VD_{ss} being slightly greater than remifentanil's.

The NONMEM analysis, although encumbered with the assumptions of compartmental analysis, illustrates the pharmacokinetic differences between remifentanil and alfentanil. The most striking difference is remifentanil's rapid clearance, a difference that, as in the moment analysis, approaches an order of magnitude. As with the moment analysis, the differences in tissue distribution were not nearly as marked.

The context-sensitive half-time simulations based on the NONMEM population parameters are perhaps the most clinically interpretable way of illustrating the pharmacokinetic differences between remifentanil and

Table 4. Pharmacodynamic Parameters

Subject No.	E_0 (Hz)		E_{max} (Hz)		γ		EC_{50} ($\text{ng} \cdot \text{ml}^{-1}$)		k_{eo} (min^{-1})		$T_{1/2}k_{eo}$ (min)	
	REMI	ALF	REMI	ALF	REMI	ALF	REMI	ALF	REMI	ALF	REMI	ALF
1	23.3	27.3	16.8	19.2	5.7	13.0	23.5	498.2	1.86	2.23	2.7	0.31
2	18.8	16.6	14.8	14.6	7.8	2.4	20.7	327.7	2.58	2.82	3.7	0.25
3	21.3	13.0	15.3	8.8	5.7	7.3	23.7	499.7	0.99	1.70	1.4	0.41
4	18.4	18.5	15.9	13.4	1.7	6.4	18.8	340.6	1.04	1.02	1.5	0.68
5	19.7	14.8	17.2	9.3	1.1	4.6	11.3	436.6	0.46	2.82	0.7	0.25
6	22.1	19.6	18.9	16.9	2.5	3.0	28.7	435.8	0.68	0.35	1.0	1.99
7	19.2	20.2	11.9	13.6	4.7	1.1	17.0	89.6	1.11	0.30	1.6	2.33
8	17.7	19.6	9.7	11.5	4.0	3.7	15.0	117.0	0.73	0.40	1.1	1.74
9	13.3	13.1	7.6	13.0	4.6	23.6	24.1	550.9	1.00	0.53	1.4	1.32
10	16.2	17.7	9.9	9.8	5.0	18.3	16.4	463.5	0.93	1.92	1.3	0.36
Mean	19.0	18.0	13.8	13.0	4.3	8.3	19.9	375.9	1.14	1.41	1.6	0.96
SD	2.9	4.2	3.8	3.3	2.0	7.5	5.2	159.3	0.62	1.02	0.9	0.81

REMI = remifentanil; ALF = alfentanil.

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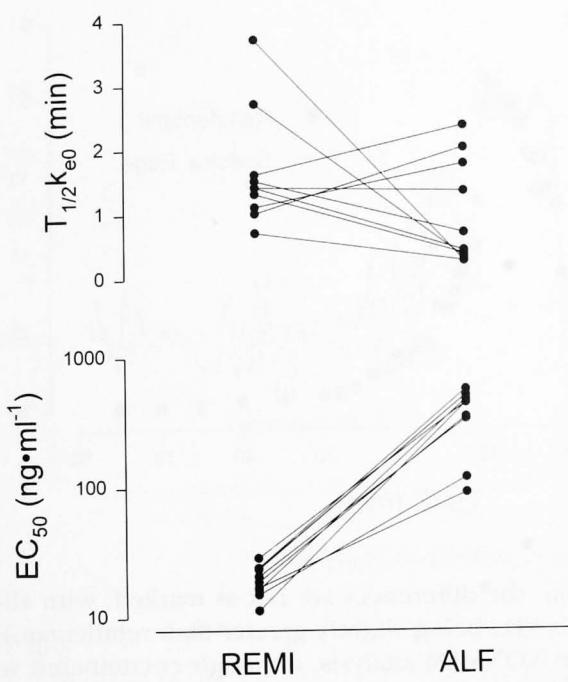


Fig. 7. The half-time for blood effect-site equilibration ($T_{1/2}k_{e0}$) as determined by a hysteresis minimization technique and the effective concentration for 50% of maximal electroencephalographic (EEG) effect (EC_{50}) as determined by nonlinear regression using a sigmoid E_{max} model. The $T_{1/2}k_{e0}$ is expressed in minutes and the EC_{50} in nanograms per milliliter. Each line connects the solid circles representing these remifentanil and alfentanil parameters in the same subject.

alfentanil. Using concepts developed by Shafer and Varvel,¹⁵ these simulations are an attempt to provide context-sensitive half-times, as proposed by Hughes *et al.*¹⁶ In this case, the "context" is the duration of a continuous infusion. Defined as the time required to achieve a 50% decrease in concentration after termination of a continuous infusion targeting a constant concentration, context-sensitive half-times are a method of providing some clinically interpretable meaning to what can be a confusing table of pharmacokinetic parameters.¹⁷ The simulations depicted in figure 4 contrast the short, time-independent context-sensitive half-time of remifentanil with the longer, time-dependent context-sensitive half-time of alfentanil (80% decrement times are also included in fig. 5).

The pharmacokinetic parameters and the related conclusions published herein for both remifentanil and alfentanil are consistent with the existing literature.^{2-4,18,19} Compared to prior reports, however, a unique feature of this study is the crossover design, enabling prospective comparison of each drug's pharmacokinetics in a single group of subjects. Prior com-

parisons of remifentanil and alfentanil pharmacokinetics have relied on literature values for alfentanil.^{2,3} The only other prospective comparison study involved smaller doses given to conscious volunteers and employed a parallel group design in which neither group received both drugs.⁴ This study is thus the first prospective, crossover confirmation of the previously re-

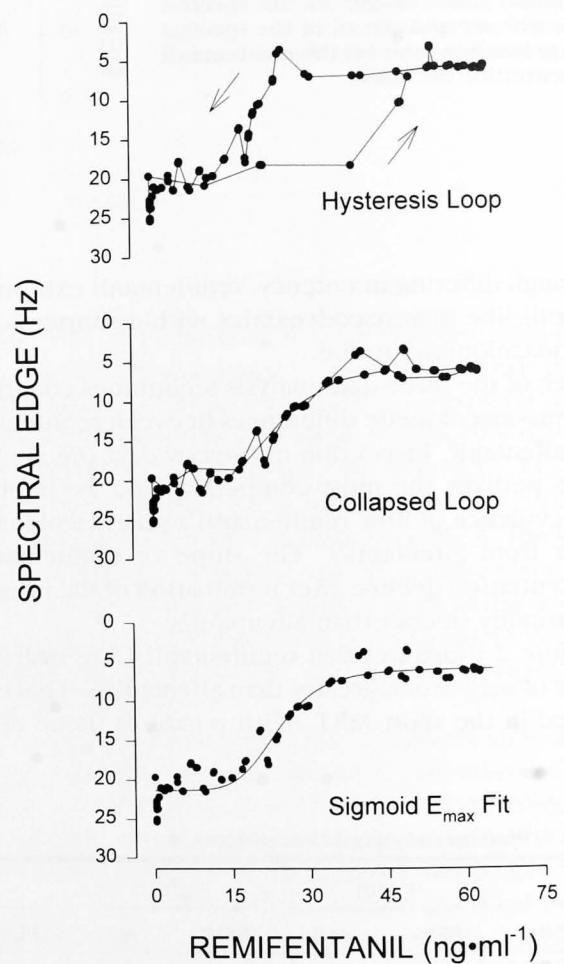


Fig. 8. A typical set of hysteresis loops and the final estimate of the concentration-effect relationship from the remifentanil limb of the study. The three sections of this figure summarize the pharmacodynamic modeling process. Each solid circle represents a single data collection point. The upper panel is a crude hysteresis loop of raw data, plotting concentration in the blood *versus* effect; the arrows indicate the time course. The middle panel is a collapsed hysteresis loop of the same data and is a result of the k_{e0} -optimizing algorithm; apparent effect-site concentration is plotted *versus* effect. The collapsed loop is a representation of the pseudosteady-state concentration-effect relationship and serves as the data set for parametric pharmacodynamic modeling. The lower panel shows a "sigmoid E_{max} " model fit to the effect-site concentration *versus* effect data.

Fig. 9. The final estimated concentration-effect relationship for remifentanil and alfentanil. The solid lines represent models between 1 and 10, dotted lines represent models between 10 and 100, bold lines portray the dynamic model for each drug. The horizontal axis is on a log scale.

ported pharmacokinetics of remifentanil and alfentanil.

The pharmacokinetic parameters of remifentanil in prior studies closely approximate those of alfentanil, with a rapid decline in blood concentration after termination of drug infusion. Pharmacokinetic simulations show that, when a rapid infusion is used, the goal is to generate a large central compartment, remifentanil having a larger pharmacokinetic parameter than alfentanil at the same concentration after termination of drug infusion.

An important limitation of this analysis is that our estimate of the pharmacokinetic parameters may not be fully accurate, as our estimates of the pharmacokinetic parameters are based on a limited number of data points.

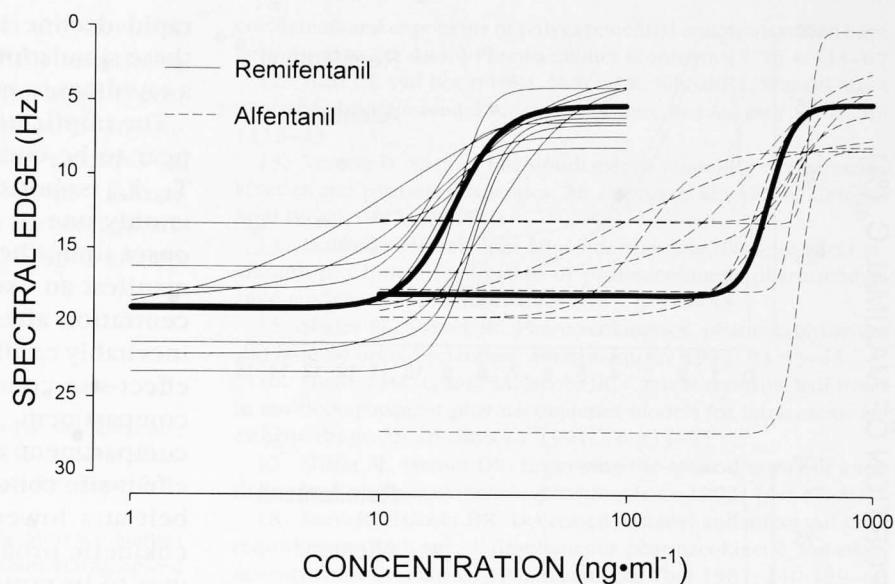
The EEG pharmacokinetic parameters were analyzed using a two-compartment model, followed by parameter estimation of the concentration-effect relationship. The pharmacokinetic parameters are 19-times greater than those of alfentanil, and by extrapolation to zero concentration, remifentanil's pharmacokinetic parameters are similar to those of alfentanil.

Inspection of the EEG waveforms reveals the nearly identical pharmacokinetic parameters for the two drugs, with remifentanil having a slightly faster onset of action than alfentanil in terms of onset speed.

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pharmacokinetic fentanyl.^{2,3} The study involved volunteers and em- neither group s the first pro- previously re-

Fig. 9. The final estimations of the concentration-effect relationship for remifentanil and alfentanil in each individual. The solid lines represent the remifentanil models between 1 and 100 ng·ml⁻¹. The dotted lines represent the alfentanil models between 10 and 1,000 ng·ml⁻¹. The bold lines portray the mean pharmacodynamic model for each drug. The horizontal axis is on a log scale.



ported pharmacokinetic differences between remifentanil and alfentanil.

The pharmacokinetic parameters estimated for remifentanil in prior studies and confirmed in this study closely approximate those theoretically required when a rapid decline in blood concentration is desired after termination of drug administration. Recent pharmacokinetic simulations by Youngs and Shafer indicate that, when a rapid decrease in blood concentration is the goal, it is beneficial to have a small central volume and a large central clearance.²⁰ From a clinical viewpoint, remifentanil possesses these desirable pharmacokinetic parameters to ensure a rapid decline in concentration after termination of an infusion.²¹

An important limitation of our pharmacokinetic analysis is that our estimates of VD_{ss} assume that all clearance occurs in the central compartment. This assumption may not be fully applicable to remifentanil. Thus, our estimates of remifentanil's VD_{ss} may be low.

The EEG pharmacodynamic data for each drug were analyzed using a hysteresis minimization technique followed by parametric modeling of the apparent concentration-effect relationship. With the exception of a 19-times greater potency, this analysis confirms remifentanil's pharmacodynamic similarity with alfentanil and, by extrapolation, the other fentanyl congeners.

Inspection of the raw pharmacodynamic data (fig. 6) reveals the nearly identical pharmacodynamic profile for the two drugs. Both exhibit identical changes in the raw EEG waveform and spectral edge parameter in terms of onset speed and magnitude of effect. Recovery

to a baseline EEG pattern, however, is more rapid with remifentanil, as judged by the raw data plots. The nature and magnitude of these EEG changes are classic for the potent μ agonists and can be viewed as the EEG fingerprint of this drug class.²²

With regard to the latency to peak effect, the hysteresis loop minimization technique results suggest that both drugs will exhibit rapid onset when administered in sufficient doses. The $t_{1/2}k_{e0}$ parameter, a factor known to be important in determining onset of peak drug effect,²³ is similar for the two drugs. This is in contrast to fentanyl and sufentanil, both of which exhibit slower equilibration between plasma and effect-site concentrations and thus are known to be drugs of relatively longer latency to peak effect unless administered in high doses.^{24,25}

The parametric modeling of the concentration-effect relationship estimated an 18.9-times greater potency of remifentanil compared to alfentanil. This finding confirms that remifentanil is moderately less potent than fentanyl.²⁴ However, in comparing the potencies of remifentanil and the other fentanyl congeners, it is important to note that the EC_{50} values for the other congeners have traditionally been reported in terms of plasma concentration.^{18,24,25} Thus, correction for the partitioning of alfentanil between whole blood and plasma using a ratio of 0.63 is necessary when making extrapolations from previously published alfentanil literature.²⁶ When comparing a remifentanil whole blood EC_{50} value from this study with a corrected plasma alfentanil EC_{50} value (596.7

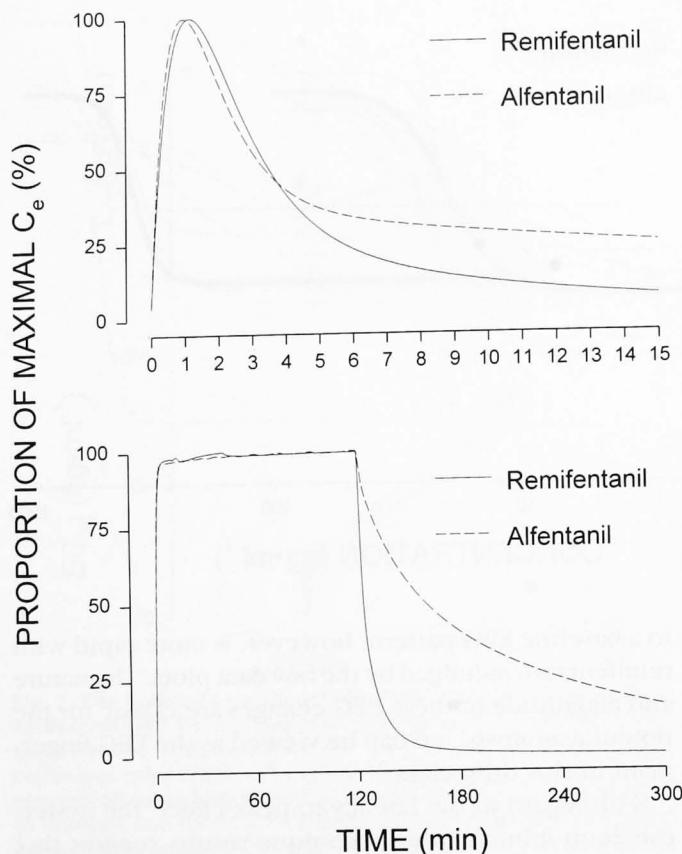


Fig. 10. Simulations of effect-site concentrations (C_e) that result from equipotent bolus and infusion doses of remifentanil and alfentanil using the complete pharmacokinetic-dynamic model. The upper panel represents the effect-site concentrations that result from equipotent bolus doses. The lower panel represents the effect-site concentrations that result from a 2-h computer-controlled infusion targeted to an EC_{50} level for each drug. The concentrations on the vertical axis are expressed as a proportion of the maximal effect-site concentration.

($\text{ng} \cdot \text{ml}^{-1}$), remifentanil is 30 times more potent than alfentanil.

The pharmacodynamic simulations are perhaps the most important means of contrasting the clinical pharmacology of the two drugs. Because they make use of the full pharmacokinetic/pharmacodynamic model, these simulations illustrate the complex interaction of all the kinetic-dynamic parameters in a clinically comprehensible way.²⁷ The simulation depicted in the upper panel of figure 10 confirms that, when administered in equipotent bolus doses, remifentanil will exhibit a short latency to peak effect that is comparable to alfentanil. The second simulation (fig. 10, lower panel) suggests that, after a 2-h equipotent infusion is terminated, remifentanil will exhibit an obviously more

rapid decline in effect-site concentration. Based on these simulations, remifentanil can be expected to be a rapid-onset, rapid-offset opioid.

The implication of the first simulation may not appear to be consistent with the fact that alfentanil's $T_{1/2}k_{e0}$ is shorter than remifentanil's. Because $T_{1/2}k_{e0}$ is only one of many factors that contribute to drug onset time, the finding is not surprising. Drugs that manifest an extremely rapid decline in plasma concentration after termination of drug administration inevitably exhibit a short time to peak effect, because effect-site concentrations are driven by the central compartment concentration gradient. If central compartment concentrations decline rapidly, peak effect-site concentration will be reached quickly, albeit at a lower peak. Thus, remifentanil's pharmacokinetic profile, in addition to its $T_{1/2}k_{e0}$, contributes to its rapid latency to peak effect. For practical purposes, the results of this study would suggest that remifentanil and alfentanil are essentially equivalent in terms of latency to peak effect; that is, both drugs should be regarded as rapid-onset agents. It should be emphasized that simulation of effect-site concentrations that result from bolus dosing are potentially limited by the fact that compartmental models do not consider the effect of recirculatory peaks.²⁸

For infusions of short duration (e.g., 10 min in this case) the pharmacokinetic differences between remifentanil and alfentanil are not readily apparent. Only after infusions of longer duration (fig. 4) do the pharmacokinetic differences become more obviously evident. The context-sensitive half-times for the currently marketed fentanyl congeners are not grossly divergent until infusions of longer than 20–30 min.¹⁵

The results of the pharmacodynamic modeling for both remifentanil and alfentanil reported here are consistent with the existing literature. A previous report of remifentanil pharmacodynamics employing an experimental pain model revealed a $t_{1/2}k_{e0}$ of 1.3 min and a 20–30-times greater potency of remifentanil compared to alfentanil.⁴ Similarly, previous reports of alfentanil pharmacodynamic parameters included $t_{1/2}k_{e0}$ values of 0.9 and 1.1 min and EC_{50} values of 479 and 520 $\text{ng} \cdot \text{ml}^{-1}$.^{18,24}

Anesthesiologists have long recognized the need for a short-acting opioid with predictable pharmacokinetics. Because the lengths of surgical procedures often are unpredictable, and because the level of surgical stimulation against which the depth of anesthesia must be balanced is highly variable and dynamic, the advan-

tages of predictability. Recent advances in opioid pharmacokinetics have trended toward predictability, including muscle relaxants and halation gases. Remifentanil is the first drug to follow this direction toward predictability. Its clinical use will depend on the advantages associated with its predictability.

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ion. Based on expected to be on may not appear at alfentanil's because $T_{1/2}k_{e0}$ contribute to drug effect. Drugs that in plasma con administration effect, because by the central t. If central rapidly, peak quickly, although alfentanil's pharmacokinetics k_{e0} , contributes. For practical purposes it suggest that equally equivalent is, both drugs agents. It should short-site concentrations potentially different models do not have peaks.²⁸

10 min in this between remifentanil and alfentanil is apparent. Only (1) do the pharmacokinetics obviously evidence for the currently grossly divergent in.¹⁵

For modeling for and here are comparative report employing an ex- k_{e0} of 1.3 min of remifentanil previous reports eters included EC₅₀ values of

the need for pharmacokinetic procedures often level of surgical anesthesia must be dramatic, the advan-

tages of predictably short-acting agents are obvious. Recent advances in drug development for anesthesia have trended toward shorter-acting agents of all types, including muscle relaxants, sedative hypnotics, and inhalation gases. Remifentanil represents an example of this direction toward shorter-acting agents. Future clinical use will determine whether the theoretical advantages associated with a short-acting opioid are realized.

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