Remifentanil Versus Alfentanil
Comparative Pharmacokinetics and Pharmacodynamics in Healthy Adult Male Volunteers

Talmage D. Egan, M.D.,* Charles F. Minto, M.D.,† David J. Hermann, Pharm.D.,‡ Juliana Barr, M.D.,§ Keith T. Muir, Ph.D.,† Steven L. Shafer, M.D.,‖

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 data, 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 (Vdss), but remifentanil’s central clearance (CL) is substantially greater. The NONMEM analysis population pharmacokinetic parameters for remifentanil include a CL of 2.9 l·min⁻¹, a Vdss of 21.8 l, and a terminal half-life of 35.1 min. Corresponding NONMEM parameters for alfentanil are 0.36 l·min⁻¹, 34.1 l, 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 T₁/₂,eq for remifentanil of 1.6 min and 0.9 min for alfentanil. However, remifentanil is 19 times more potent than alfentanil, with an effective concentration for 50% maximal effect of 19.9 ng·ml⁻¹ versus 375.9 ng·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: Anesthesia, 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.)

REMIFENTANIL (hydrochloride salt of 3-[4-methoxy-carbonyl-4-[1-oxopropyl]phenylamino]-1-piperidinopropanoic acid, methyl ester), formerly known as GI87084B, is a synthetic opioid that exhibits classic μ-agonist pharmacologic effects. 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. The aim of this study was to contrast the clinical pharmacology of remifen-
tanium 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 I 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. Four channels (F3-P3, F4-P4, P3-C3, P4-C4) 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 nonrebreathing 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 µg·kg⁻¹·min⁻¹ (except the first subject, who received 2 µg·kg⁻¹·min⁻¹), and alfentanil was administered at 1.500 µg·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. 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 ng·ml⁻¹ and an interassay 15% for concentration. Deuterated remifentanil was added to the samples in recovery. Alfentanil blood was analyzed by gas chromatography with an interassay 10% and a quantitation limit of 0.1 ng·ml⁻¹.

**EEG Signal Processing**

The digitized raw EEG was uploaded to a computer for analysis. EEG raw data were band-pass filtered digitally with a 50-Hz low cutoff and a 2.5-Hz high cutoff. Spectral analysis was performed by fast Fourier transform. Amplitudes of the principal frequencies were measured, and the energy was calculated. The area under the power spectrum density (PSD) curve for each frequency band was determined.

**Pharmacokinetics**

The pharmacokinetic parameters were described by a two-compartment open model as the number of compartments that best described the data. A computerized nonlinear, least-squares fitting program was used to estimate the pharmacokinetic parameters and their variances. The noncompartmental analysis, computerized method was based on the pharmacokinetic parameters of the fitted pharmacokinetic model.

**Moment Analysis**

The moments to phase-displacement (PD) and moment analyses were calculated. The mean PD, the area under the concentration-time curve (AUC), and the standard deviation of the area under the curve (SDAUC) were calculated for each subject. The relationships between these parameters were analyzed to determine the appropriate pharmacokinetic parameters for the analysis of the pharmacokinetic parameters of the fitted pharmacokinetic model.
and an interassay coefficient of variation of less than 15% for concentrations greater than 0.1 ng·mL⁻¹. Tert-
butylated remifentanil was included in the collection tubes as an internal standard to correct for varia-
tions 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 ng·mL⁻¹.⁷ Fentanyl
was included as an internal standard.

EEG Signal Processing
The digitized raw EEG data were processed by com-
puter 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 am-
plitudes of the individual frequency components. Fin-
ally, 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 pharma-
cokinetic 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 pharma-
cokinetic parameters were performed.

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

concentration (Cₘ) versus time (t) plot using the trap-
pezoidal method with linear interpolation when concen-
trations 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 Vₐₐ, 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 pharma-
cokinetic parameters for both drugs were estimated using
the NONMEM approach. Because it had been previ-
ously demonstrated for the remifentanil dose range studied,
linear pharmacokinetics was assumed for the purposes of
this analysis.² In contrast with the two-stage ap-
proach, wherein the population pharmacokinetic model
is obtained by averaging the parameters estimated
from individuals, NONMEM simultaneously anal-
lyzes an entire population’s data and provides esti-
mates of typical values for the pharmacokinetic param-
eters 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:

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

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

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

The performance of the population models con-
bstructed by NONMEM for both drugs was assessed in
terms of the ability to predict the measured blood con-
centrations. 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, Uni-
versity of California, San Francisco, 1979

Anesthesiology, V 84, No 4, Apr 1996
\[ WR = \frac{C_m - C_p}{C_p} \]

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:

\[ \text{MDAWR} = \text{median} \{ |WR_1|, |WR_2|, \ldots, |WR_n| \} \]

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 this 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 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 concentration-effect relationship were sigmoid in nature, a logistic-like equation (i.e., Hill-Sigma) relationship parameterized by the least squares nonlinear equation was applied to a spreadsheet (Microsoft Excel).

\[ E = \frac{E_{\text{max}}}{1 + (C / \gamma)^n} \]

where \( E \) is the percent effect, \( E_{\text{max}} \) is the maximal effect, \( C \) is the measured concentration, \( \gamma \) is a measure of concentration at one half the maximal effect, and \( n \) is a concentration depression parameter modeling the extent of a predicted effect. Asymmetric sigmoidal curves were fitted to the data for remifentanil and alfentanil.

**Computer Simulations.** Computer simulations were performed using the logistic-like equation application of the concentration-effect relationship, intended to simulate, the administration of equipotent doses of remifentanil and alfentanil. The computer simulation program was written in Fortran 80 with a computer-controlled printer (University, Palomar).
### Table 1. Moment Analysis Pharmacokinetic Parameters

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

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

Effect relationship determined by the estimation of \( k_{01} \) were sigmoid in shape, an inhibitory "sigmoid \( E_{max} \)" equation (i.e., Hill equation) was used to model the relationship parametrically. 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, \( E_0 \) is the baseline effect level, \( E_{max} \) is maximal effect, \( C_e \) is effect-site concentration, \( \gamma \) is a measure of curve steepness, and \( EC_{50} \) 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 equipotent doses (185 \( \mu \)g remifentanil, 3,500 \( \mu \)g 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 \( EC_{50} \) 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 \( \pm \) 4.8 yr, weight of 83.5 \( \pm \) 11.2 kg, and height of 183.7 \( \pm \) 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-
Table 2. NONMEM Three-compartment Population Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remifentanil</th>
<th>Alfentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional coefficients</td>
<td>0.85</td>
<td>0.81</td>
</tr>
<tr>
<td>A</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>B</td>
<td>0.002</td>
<td>0.05</td>
</tr>
<tr>
<td>Hybrid rate constants (min⁻¹)</td>
<td>0.7521</td>
<td>0.9480</td>
</tr>
<tr>
<td>α</td>
<td>0.1097</td>
<td>0.0426</td>
</tr>
<tr>
<td>β</td>
<td>0.0197</td>
<td>0.0073</td>
</tr>
<tr>
<td>Micronate constants (min⁻¹)</td>
<td>0.3847</td>
<td>0.0880</td>
</tr>
<tr>
<td>k10</td>
<td>0.2569</td>
<td>0.6161</td>
</tr>
<tr>
<td>k12</td>
<td>0.0128</td>
<td>0.0709</td>
</tr>
<tr>
<td>k13</td>
<td>0.2066</td>
<td>0.2066</td>
</tr>
<tr>
<td>k21</td>
<td>0.0205</td>
<td>0.0163</td>
</tr>
<tr>
<td>Half-lives (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>β</td>
<td>6.3</td>
<td>16.3</td>
</tr>
<tr>
<td>γ</td>
<td>35.1</td>
<td>94.5</td>
</tr>
<tr>
<td>Volumes (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>7.6 (0.32)</td>
<td>4.1 (0.33)</td>
</tr>
<tr>
<td>Peripheral 1</td>
<td>9.4</td>
<td>12.2</td>
</tr>
<tr>
<td>Peripheral 2</td>
<td>4.7</td>
<td>17.8</td>
</tr>
<tr>
<td>Steady state</td>
<td>21.8</td>
<td>34.1</td>
</tr>
<tr>
<td>Clearances (L·min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>2.92 (0.12)</td>
<td>0.36 (0.22)</td>
</tr>
<tr>
<td>Intercompartmental 1</td>
<td>1.96</td>
<td>2.52</td>
</tr>
<tr>
<td>Intercompartmental 2</td>
<td>0.10</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values in parentheses are coefficient of variation.

Table 3. NONMEM Three-compartment Population Model Weighted Residuals

<table>
<thead>
<tr>
<th>Residuals</th>
<th>Median (MDAWR)</th>
<th>10th Percentile</th>
<th>90th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remifentanil</td>
<td>15.9</td>
<td>3.3</td>
<td>39.9</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>13.2</td>
<td>2.6</td>
<td>40.0</td>
</tr>
</tbody>
</table>

MDAWR = median absolute weighted residual.

Fig. 2. The clearance (CL), mean residence time (MRT), and volume of distribution at steady-state (VDs) of remifentanil (REMI) versus alfentanil (ALF) as determined by moment analysis. CL is expressed in liters per minute, MRT in minutes, and VDs 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.

Fig. 3. The residual analysis models considered as defined in the text represents the performance applied to an individual patient where concentrations were postulated as represented by a set of magnitude. The mean and the standard error for each drug estimate are shown in table 4.

The performance of each drug is represented for compartmental volume of approximately 1.5 L, along with the 1.5 L steady state volume in table 3. Figure 3 of these NONMEM simulations demonstrates the systematic bias, the bias that is first few minutes and is then reduced over the end of sample time simulations.
REMIFENTANIL VERSUS ALFENTANIL

REMIFENTANIL VERSUS ALFENTANIL

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.

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.

K₀ 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 k₀ values. Remifentanil’s T₁/₂k₀ is 1.6 min; alfentanil’s is 0.96 min. The k₀ and T₁/₂k₀ values for each subject are shown in table 4. The upper panel of figure 7 contrasts the T₁/₂k₀ 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 7. Figure 8 illustrates how the k₀-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

Anesthesiology, V 84, No 4, Apr 1996
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. 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.

Table 4. Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>REMI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23.5</td>
</tr>
<tr>
<td>2</td>
<td>16.5</td>
</tr>
<tr>
<td>3</td>
<td>21.2</td>
</tr>
<tr>
<td>4</td>
<td>18.3</td>
</tr>
<tr>
<td>5</td>
<td>11.9</td>
</tr>
<tr>
<td>6</td>
<td>22.1</td>
</tr>
<tr>
<td>7</td>
<td>19.4</td>
</tr>
<tr>
<td>8</td>
<td>18.9</td>
</tr>
<tr>
<td>9</td>
<td>14.7</td>
</tr>
<tr>
<td>10</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Mean 15.5  SD 4.5

Alfentanil 80%
Alfentanil 50%
Remifentanil 50%
Remifentanil 80%

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\textsubscript{50} values. Remifentanil's mean EC\textsubscript{50} is 19.9 ng·ml\textsuperscript{-1} compared with 375.9 ng·ml\textsuperscript{-1} for alfentanil. EC\textsubscript{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\textsubscript{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,
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 VDₚ 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 alfentanil in a limited number of volunteers using a balanced design. In summary,

### Table 4. Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Subject No</th>
<th>Eₒ(10⁻² Hz)</th>
<th>Eₘₕ(10⁻² Hz)</th>
<th>γ</th>
<th>EC₅₀ (ng·ml⁻¹)</th>
<th>kₑₕ (min⁻¹)</th>
<th>Tₑₕkₑₕ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REMI</td>
<td>ALF</td>
<td>REMI</td>
<td>ALF</td>
<td>REMI</td>
<td>ALF</td>
</tr>
<tr>
<td>1</td>
<td>23.3</td>
<td>27.3</td>
<td>16.8</td>
<td>19.2</td>
<td>5.7</td>
<td>13.0</td>
</tr>
<tr>
<td>2</td>
<td>18.8</td>
<td>16.6</td>
<td>14.8</td>
<td>14.6</td>
<td>7.8</td>
<td>2.4</td>
</tr>
<tr>
<td>3</td>
<td>21.3</td>
<td>13.0</td>
<td>15.3</td>
<td>8.8</td>
<td>5.7</td>
<td>7.3</td>
</tr>
<tr>
<td>4</td>
<td>18.4</td>
<td>18.5</td>
<td>15.9</td>
<td>13.4</td>
<td>1.7</td>
<td>6.4</td>
</tr>
<tr>
<td>5</td>
<td>19.7</td>
<td>14.8</td>
<td>17.2</td>
<td>9.3</td>
<td>1.1</td>
<td>4.6</td>
</tr>
<tr>
<td>6</td>
<td>22.1</td>
<td>19.6</td>
<td>18.9</td>
<td>16.9</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>7</td>
<td>19.2</td>
<td>20.2</td>
<td>11.9</td>
<td>13.6</td>
<td>4.7</td>
<td>1.1</td>
</tr>
<tr>
<td>8</td>
<td>17.7</td>
<td>19.6</td>
<td>9.7</td>
<td>11.5</td>
<td>4.0</td>
<td>3.7</td>
</tr>
<tr>
<td>9</td>
<td>13.3</td>
<td>13.1</td>
<td>7.6</td>
<td>13.0</td>
<td>4.6</td>
<td>23.6</td>
</tr>
<tr>
<td>10</td>
<td>16.2</td>
<td>17.7</td>
<td>9.9</td>
<td>9.8</td>
<td>5.0</td>
<td>18.3</td>
</tr>
<tr>
<td>Mean</td>
<td>19.0</td>
<td>18.0</td>
<td>13.8</td>
<td>13.0</td>
<td>4.3</td>
<td>8.3</td>
</tr>
<tr>
<td>SD</td>
<td>2.9</td>
<td>4.2</td>
<td>3.8</td>
<td>3.3</td>
<td>2.0</td>
<td>7.5</td>
</tr>
</tbody>
</table>

REMI = remifentanil; ALF = alfentanil.
comparisons of remifentanil and alfentanil pharmacokinetics have relied on literature values for alfentanil. 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. This study is thus the first prospective, crossover confirmation of the previously reported pharmacokinetics of remifentanil and alfentanil.

The pharmacokinetic parameters and the related conclusions published herein for both remifentanil and alfentanil are consistent with the existing literature. 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 comparison 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 \( k_{\text{ao}} \)-optimizing algorithm; apparent effect-site concentration is plotted versus effect. The collapsed loop is a representation of the pseudo-steady-state concentration-effect relationship and serves as the data set for parametric pharmacodynamic modeling. The lower panel shows a sigmoid \( E_{\text{max}} \) model fit to the effect-site concentration versus effect data.
REMITFANIL VERSUS ALFENTANIL

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.

port, 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. From a clinical viewpoint, remifentanil possesses these desirable pharmacokinetic parameters to ensure a rapid decline in concentration after termination of an infusion.

An important limitation of our pharmacokinetic analysis is that our estimates of VDₘ assume that all clearance occurs in the central compartment. This assumption may not be fully applicable to remifentanil. Thus, our estimates of remifentanil’s VDₘ 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. 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 t₁₀₀₀₉₀ parameter, a factor known to be important in determining onset of peak drug effect, 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.

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. However, in comparing the potencies of remifentanil and the other fentanyl congeners, it is important to note that the EC₅₀ values for the other congeners have traditionally been reported in terms of plasma concentration. Thus, correction for the partitioning of alfentanil between whole blood and plasma using a ratio of 0.65 is necessary when making extrapolations from previously published alfentanil literature. When comparing a remifentanil whole blood EC₅₀ value from this study with a corrected plasma alfentanil EC₅₀ value (596.7
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 $T_{1/2}k_{ho}$ is shorter than remifentanil’s. Because $T_{1/2}k_{ho}$ 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 $T_{1/2}k_{ho}$, 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.

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.

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 $t_{1/2}k_{ho}$ of 1.3 min and a 20–30-times greater potency of remifentanil compared to alfentanil. Similarly, previous reports of alfentanil pharmacodynamic parameters included $t_{1/2}k_{ho}$ values of 0.9 and 1.1 min and $EC_{50}$ values of 479 and 520 ng·ml$^{-1}$.

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-

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-pharmacodynamic 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.

ng·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. 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

References
7. Levy WR, Shapiro TH: Pecs: personal computer software for the calculation of many

Anesthesiology. V 84, No 4, Apr 1996
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.

References
3. Westmoreland CL, Hoke JF, Sebel PS, Hug CC, Mui KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology 1993; 79:893–905
11. Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polynoexponential equations which have been fitted to the data. J Pharmacokin Biopharm 1976; 4:445–67