The Pharmacokinetics of the New Short-acting Opioid Remifentanil (GI87084B) in Healthy Adult Male Volunteers

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Background: Remifentanil (GI87084B) is a new short-acting opioid with a unique ester structure. Metabolism of remifentanil by ester hydrolysis results in very rapid elimination. The aim of this study was to characterize in detail the pharmacokinetic profile of remifentanil in healthy male volunteers.

Methods: Ten healthy adult male volunteers received a zero-order infusion of remifentanil at doses ranging from 1 to 8 μg·kg⁻¹·min⁻¹ for 20 min. Frequent arterial blood samples were drawn and analyzed by gas chromatographic mass spectrometry to determine the remifentanil blood concentrations. The raw pharmacokinetic data were analyzed using three different parametric compartmental modeling methods (traditional two-stage, naive pooled data, and NONMEM). The raw pharmacokinetic data also were analyzed using numeric deconvolution and a nonparametric moment technique. A computer simulation using the pharmacokinetic parameters of the NONMEM compartmental model was performed to provide a more intuitively meaningful and clinically relevant description of the pharmacokinetics. The simulation estimated the time necessary to achieve a 50% decrease in remifentanil concentration after a variable-length infusion.

Results: For each parametric method, a three-compartment mamillary model that accurately describes remifentanil’s concentration decay curve was constructed. The NONMEM analysis population pharmacokinetic parameters included a central clearance of 2.8 l/min, a volume of distribution at steady state of 32.8 l, and a terminal half-life of 48 min. The mean results of the nonparametric moment analysis included a clearance of 2.9 l/min, a volume of distribution at steady state of 31.8 l, and a mean residence time of 10.9 min. The computer simulation revealed the strikingly unique pharmacokinetic profile of remifentanil compared to that of the currently available fentanyl family of opioids.

Conclusions: Remifentanil is a new, short-acting opioid with promising clinical potential in anesthesia. (Key words: Analgesics, opioids; GI87084B, remifentanil. Pharmacokinetics: GI87084B, population; remifentanil.)

REMIFENTANIL (hydrochloride salt of 3-[4-methoxy-carbonyl-4-(1-oxopropyl)phenylamino]-1-piperidinepropanoic acid, methyl ester), formerly known as GI87084B, is a new synthetic opioid that exhibits classic μ-agonist pharmacologic effects including analgesia, sedation, and respiratory depression.1 While chemically related to the fentanyl family of short-acting piperidine derivatives commonly used as supplements to general anesthesia, remifentanil is structurally unique among currently available opioids because of its ester linkage. Remifentanil’s ester structure renders it susceptible to hydrolysis by blood and tissue nonspecific esterases, resulting in very rapid degradation to essentially inactive metabolites as in figure 1. Remifentanil thus may constitute the first true ultra-short-acting opioid for use as a supplement to general anesthesia. A detailed pharmacokinetic model charac-
Characterizing the disposition of remifentanil in healthy volunteers has not been described.

The aim of this study was to characterize the pharmacokinetics of remifentanil in healthy male volunteers using frequent arterial blood sampling and computer-assisted pharmacokinetic modeling techniques. The intent was to provide a part of the basic pharmacology database necessary to evaluate remifentanil’s clinical potential and to guide future study of this new compound. In an effort to provide the most accurate and complete description of the pharmacokinetics possible, a wide variety of analysis techniques were used.

Materials and Methods

Pretreatment, Treatment, and Post-treatment Phases

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 men between the ages of 18 and 40 yr without history of significant medical illness 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/day, a history of hypersensitivity to opioids, or a record of significant psychiatric disease.

Before the study day, each subject was instructed to abstain from ingesting any over-the-counter medication within 3 days of the study. Volunteers were also asked to abstain from alcohol for at least 24 h before the study time. In addition, subjects were not permitted to have anything by mouth or smoke cigarettes for 12 h before beginning the study.

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 the purpose of blood sampling and continuous blood pressure monitoring. A solution of normal saline was infused at an approximate rate of 60 ml/h. Safety monitors included a continuous five-lead electrocardiogram, continuous pulse oximetry, and a precordial stethoscope.

Before drug administration, the volunteers received 0.2 mg glycopyrrolate intravenously to prevent opioid-induced bradycardia and 0.5 mg pancuronium intravenously to mitigate opioid-induced rigidity. Volunteers breathed 100% O₂ by face mask delivered via a nonbreathing circuit.

Remifentanil was administered intravenously as a zero-order infusion by a laboratory syringe pump (Har-
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The first pair of volunteers received remifentanil at a rate of 1 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \). In subsequent volunteers, the dose administered was gradually increased, reaching a maximum of 8 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \).

Three-milliliter 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 0 to 5 min, every minute from 6 to 10 min, and every 2 min from 12 to 20 min. After stopping the infusion, samples were again collected every 30 s from 0 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 stopping the infusion.

During the remifentanil infusion, the volunteer’s ventilation was assisted by bag and mask with 100% O\(_2\) 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 samples confirmed the adequacy of ventilation and oxygenation.

Volunteers were monitored after the end of the infusion for at least 3 h. Heart rate and arterial blood pressure data were continuously monitored and digitally stored. Nausea and/or vomiting were treated as necessary by an intravenous injection of 10 mg metoclopramide.

Volunteers were monitored for adverse events throughout the treatment phase. When adverse events occurred, details of the event were recorded immediately. Subjectively experienced complications such as nausea were rated by the volunteer in terms of severity, whereas observed adverse events such as vomiting were rated by the investigators. Muscular rigidity, for example, was assessed by the investigators and was graded as mild, moderate, or severe, depending on the difficulty encountered with bag and mask ventilation.

After completion of the treatment phase, each volunteer was admitted to an inpatient unit for observation overnight. The next morning, the volunteers were questioned again regarding any adverse events associated with the study.

**Blood Sample Processing and Concentration Assay**

Because of remifentanil’s metabolic degradation pathway, special processing was necessary to prevent continued metabolism of remifentanil after sample collection. The process consisted of immediate arrest of esterase activity in the blood sample followed by extraction of remifentanil into an organic solvent. Blood esterase activity was initially inactivated by the addition of acetonitrile, a water-soluble compound that rapidly precipitates plasma proteins. Methylene chloride was subsequently added to the blood-acetonitrile mixture to extract the remifentanil into the organic phase. The organic phase was then separated and stored at −70°C until the time of assay.

Remifentanil blood concentrations were measured by a high-resolution, gas chromatographic, mass spectrometry assay with a quantitation limit of 0.1 ng/ml and a paired aliquot coefficient of variation of less than 15% for concentrations greater than 0.1 ng/ml.

**Pharmacokinetic Analysis**

To provide as complete and accurate a description as possible in this initial report, the pharmacokinetics of remifentanil were analyzed by a wide variety of methods. Because linear pharmacokinetics is a fundamental assumption of the other methods used, an analysis for linearity was initially completed. A classic moment analysis (analysis of area under the curve) was then done to calculate the model independent pharmacokinetic parameters. Subsequently, three distinct regression approaches were used to estimate the compartmental model pharmacokinetic parameters: the two-stage (TS) approach, a naive pooled data (NPD) approach, and a mixed-effect population approach based on the NONMEM program (University of California, San Francisco, San Francisco, California). The TS and NPD approaches were included because they are familiar to most investigators and are easy to perform with standard nonlinear regression programs. The mixed-effect population approach, viewed by many as the optimal population modeling method, is computationally more intensive and is unique in that it provides estimates of both intraindividual and interindividual pharmacokinetic variability. The NONMEM approach was included to determine whether additional accuracy could be gained from use of the more computationally demanding method. To visually contrast the three sets of compartmental model parameter estimates with a model-independent representation of remifentanil’s pharmacokinetics, a deconvolution analysis was done. Finally, in an effort to make some clinical sense of the rather complex pharmacokinetic
analysis, a computer simulation based on the NONMEM pharmacokinetic parameters was performed.

**Linearity Analysis.** Before a pharmacokinetic model can be said to characterize the disposition of a drug in the body for various dosage regimens, the linearity of the system must be confirmed. This was done by plotting the dose normalized concentration versus time data and visually verifying that, over the range of doses studied, there was no substantial change in the shape of the concentration versus time curve.

**Moment Analysis.** Applying the theory of statistical moments to pharmacokinetics, a nonparametric moment analysis was performed to calculate the clearance, mean residence time, and apparent volume of distribution at steady state. The area under the concentration versus time curve was calculated for each blood concentration (C₀) versus time (t) plot using a Lagrange polynomial interpolation-integration method. The terminal slope for each data set was estimated by log-linear regression after visually identifying the terminal portion of each curve.

Using the equation:

\[ \text{CL} = \frac{\text{Dose}}{\text{AUC}} \]

the clearance (CL) was calculated for each subject.

Having determined the area under the concentration versus time curve (AUC), the C₀·t versus t curve (the first moment curve), was plotted and the area under the moment curve (AUMC) was calculated. The equation

\[ \text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \]

where MRT₁ is the mean residence time of the infusion input (infusion time/2), was used to calculate the mean residence time.

Similarly, the apparent volume of distribution at steady state (VDₘₐₓ) was calculated using the equation:

\[ \text{VDₘₐₓ} = \text{CL} \cdot \text{MRT} \]

The population parameter estimates for the moment analysis were calculated by determining the mean of the individual subject values.

**Individual Compartmental Analysis.** Using MKMODEL (Elsevier, New York), an extended least-squares nonlinear regression program, we fit two- and three-compartment mamillary models to the C₀ versus t data to estimate the pharmacokinetic parameters for each volunteer individually. Extended least-squares nonlinear regression employs a likelihood-based objective function that is related to ordinary least squares, but wherein a model for the variance of the data is included so that the objective function weights each squared deviation by the expected variance. These biexponential and triexponential disposition equations were parameterized in terms of clearances and apparent distribution volumes. Because the magnitude of the errors between the measured concentrations (Cₘ) and the concentrations predicted (Cₚ) by the model were presumed to be proportional to the predicted concentration, a proportional \((1/Cₚ^2)\) variance model was used for each fit. With this choice of variance model, the extended least squares objective function minimized by MKMODEL is closely related to the sum of squared percent errors. In addition, for the two-compartment fits, a constant was added to the variance model \((\text{variance} = \text{constant} + 1/Cₚ^2)\). This constant was an estimated parameter.

After obtaining estimates for the respective volumes and clearances from nonlinear fitting, the alternative two- and three-compartment mamillary model parameters (micro and macro rate constants) for each individual were calculated using standard equations. The population parameters were determined using a TS approach in which the individual fitted parameters (in this case, clearances and apparent distribution volumes) from each nonlinear curve fit were averaged, and the remaining parameters were calculated. This method is called a TS approach because the analysis proceeds in two stages: pharmacokinetic parameters are first estimated for each individual, and these individual parameters subsequently are averaged to obtain the mean population estimate.

The adequacy of the two- and three-compartment mamillary models for each data set was contrasted using F-ratio hypothesis testing, 95% confidence interval comparisons, and visual inspection of the predicted versus the observed data plots. For the F-ratio test, a log likelihood increase of at least 4 was used as evidence favoring the more complex three-compartment model. For confidence interval comparison, after computing the 95% confidence interval of each fitted parameter (clearances and apparent distribution volumes) for both models, a parameter confidence interval from the three-compartment model that included zero was considered evidence favoring the simpler, two-compartment model.
The quality of the TS population models also was assessed in terms of the ability to predict the measured plasma concentrations. The performance of the pharmacokinetic model was quantified in terms of weighted residuals (WR). Weighted residuals measure the difference between a measured blood concentration ($C_m$) and the model predicted concentration ($C_p$) in terms of $C_p$. Thus, expressed as a percentage, WR can be defined as:

$$ WR = \frac{C_m - C_p}{C_p} \times 100. $$

Using this definition, the WR for the TS two- and three-compartment population models were computed at every measured data point.

Making use of the WR data, the overall inaccuracy of the model was determined by computing the median absolute weighted residual (MDAWR), defined as:

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

where $n$ is the total number of samples in the study population. Using this formula, the MDAWRs for the TS two- and three-compartment models were computed.

**Pooled Compartmental Analysis.** Using the same nonlinear regression techniques, including the same parameterization and variance model, a pooled fit also was performed in which a single best estimate of the population pharmacokinetic parameters was obtained in all individuals simultaneously. This kind of simultaneous pooled fit, and various modifications of it, is sometimes referred to as an NPD approach. Implementing this approach required minor modifications of MKMODEL to allow a pooled, simultaneous fit of the entire data set while incorporating individual drug dosage input for each subject. We applied this approach to both two- and three-compartment mamillary models.

Techniques identical to those implemented for the TS approach were used to calculate the remaining pharmacokinetic parameters. The adequacy of the two- and three-compartment models was compared using F-ratio hypothesis testing. The performance of the NPD population model was assessed by computing the WR and MDAWR.

**Nonlinear Mixed Effects Model Compartmental Analysis.** The population pharmacokinetic parameters also were estimated using the NONMEM program. In contrast with the TS approach in which 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.

Two- and three-compartment pharmacokinetic models were fit to the remifentanil concentration *versus* time data. These models were parameterized in terms of clearances and apparent distribution volumes assuming a log-normal distribution of residual error. NONMEM estimated the volumes and clearances of the three compartments using a model written by the authors (S.L.S.). Interindividual error on each parameter was modeled using a log-linear error model:

$$ TV = \beta e^\eta $$

where $TV$ is the true value in the individual, $\beta$ is the population mean estimate, and $\eta$ is a random variable whose distribution is estimated by NONMEM with a mean of zero and a variance of $\omega$. The estimates of $\omega$ are similar to the coefficient of variation used in standard descriptive statistics.

Techniques identical to those implemented for the NPD approach were used to calculate the remaining pharmacokinetic parameters and to compare the adequacy of the two- and three-compartment models. The performance of the NONMEM population model was assessed by computing the WR and MDAWR when the NONMEM parameters were applied to each data set.

### Table 1. Volunteer Demographics

<table>
<thead>
<tr>
<th>Subject (number)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BSA (m²)</th>
<th>LBM (kg)</th>
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<td>25</td>
<td>83</td>
<td>175</td>
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<tr>
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<td>79</td>
<td>176</td>
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<td>61</td>
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<tr>
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<td>8</td>
<td>0.1</td>
<td>6</td>
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</table>

BSA = body surface area; LBM = lean body mass.

Deconvolution Analysis. The plasma concentration versus time curves were deconvolved against the infusion input using the technique of Verotta.7 The disposition curve was constrained to be positive and non-increasing. The resulting disposition curves over time were compared visually with the estimates of the unit disposition curves from the three parametric modeling techniques (TS, NPD, and NONMEM).

Computer Simulations. Computer simulations using the pharmacokinetic parameters obtained from the NONMEM three-compartment analysis were performed to provide a graphic illustration of the predicted decline in blood concentrations when remifentanil is administered by infusion. For comparison purposes, identical simulations were performed for fentanyl, alfentanil, and sufentanil using pharmacokinetic parameter estimates obtained from the relevant literature.8,9 These simulations predict the time necessary to achieve a 50% decrease in drug concentration in the blood (or plasma) after termination of a variable-length infusion. All simulations were performed on an 80486 computer running MS-DOS (Microsoft, Redmond, WA) using programs written in C language. The simulations are based on Euler’s solution to the two- and three-compartment model with a step size of 1 s.

Results

Pretreatment, Treatment, and Post-treatment Phases

All ten volunteers originally enrolled completed the study. The volunteers were comparable in terms of age group, degree of lean body mass, and ASA physical status. The demographics of the volunteers are summarized in table 1.

All subjects received the full 20-min infusion of remifentanil. As illustrated in table 2, with the exception of muscular rigidity and nausea/vomiting, there were no significant or unexpected complications associated with remifentanil administration over a large dose range. In particular, there were no untoward hemodynamic events, such as severe bradycardia, tachycardia, or hypotension, requiring therapy or termination of the infusion. Each volunteer reported a subjective experience consistent with typical opioid pharmacodynamics, including sedation, a sensation of well-being, and/or mild euphoria. There were no dysphoric reactions. Each subject developed mild to moderate muscular rigidity requiring a brief period of succinylcholine administration by continuous infusion to facilitate controlled ventilation. Nausea and/or vomiting developed in seven of ten subjects; five of these volunteers suffered nausea and/or vomiting of sufficient degree to require therapy with metoclopomide. All subjects showed evidence of ventilatory depression manifested by mild hypercarbia on serial arterial blood gases taken during the immediate postinfusion period. No significant adverse effects were noted during the follow-up period.

Linearity Analysis. Figure 2 shows the raw concentration versus time data and the dose-normalized concentration versus time data. The dose-normalized plot reveals an apparently linear system in which, over the dose range studied, there was no grossly detectable change in the shape of the concentration decay curve.

<table>
<thead>
<tr>
<th>Subject (number)</th>
<th>Remifentanil (µg·kg⁻¹·min⁻¹)</th>
<th>Rigidity (+/−)</th>
<th>Succinylcholine (mg)</th>
<th>Nausea (+/−)</th>
<th>Vomiting (+/−)</th>
<th>Metoclopomide (mg)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>70</td>
<td>+</td>
<td>+</td>
<td>0</td>
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<td>++</td>
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</tr>
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<td>NA</td>
<td>70</td>
<td>40</td>
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− = none; + = mild; ++ = moderate; +++ = severe; NA = not applicable.
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Fig. 2. The raw and dose normalized concentration versus time data. Each line represents one volunteer. The vertical axis, representing remifentanil blood concentration, is on a log scale. As illustrated by the raw data plot, volunteers who received the lowest dose (1 μg·kg⁻¹·min⁻¹) and thus reached the lowest peak blood concentrations are represented by the solid lines; volunteers who received the highest dose (8 μg·kg⁻¹·min⁻¹) are represented by the dotted lines. Volunteers receiving intermediate doses are represented by dashed lines with progressively smaller dashes as the dose increases. The dose-normalized data plot demonstrates that the shape of the concentration decay curve does not change substantially over the dose range studied.

On this basis, for compartmental modeling purposes, linear pharmacokinetics were assumed.

Moment Analysis. The individual and average values for clearance, mean residence time, and apparent volume of distribution at steady state are shown in table 3. For both the area under the concentration versus time curve and the area under the moment curve plots, the proportion of the total curve area under measured data was large.

Individual Compartmental Analysis. Based on the results of the F-ratio test and confidence interval comparison, we found that a three-compartment mammary model was necessary to describe the blood concentra-

![Graph showing raw and normalized data](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931316/)

### Table 3. Nonparametric Moment Analysis Pharmacokinetics

<table>
<thead>
<tr>
<th>Subject (number)</th>
<th>Clearance ([l/min])</th>
<th>MRT (min)</th>
<th>VDss (l)</th>
<th>AUC under Data (%)</th>
<th>AUMC under Data (%)</th>
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<td>10.9</td>
<td>31.8</td>
<td>98.9</td>
<td>88.6</td>
</tr>
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</table>

MRT = mean residence time; VDss = volume of distribution at steady state; AUC = area under the curve; AUMC = area under the moment curve.

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the population parameter values, no standard deviations are reported.

As observed with the TS analysis, the three-compartment model was slightly more accurate than the two-compartment model, particularly in describing the terminal slope. The middle panel of figure 3 shows the WR for the three-compartment NPD model when applied to each data set. As shown in table 5, the MDAWR for the three-compartment model was 15.6%. The performance of the NPD model is illustrated in the middle panels of figure 4, which show the best, median, and worst performances of the NPD model when applied to the individual data sets.

**Nonlinear Mixed Effects Model Compartmental Analysis.** The parameters for the three-compartment models estimated using the NONMEM approach are shown in table 4. In concert with the other modeling approaches, we found the three-compartment model to be superior to the two-compartment model on the basis of F-ratio hypothesis testing. The lower panel of figure 3 plots the WR for the three-compartment NONMEM model. As noted in table 5, the MDAWR for the three-compartment model was 14.8%. The right panels of figure 4 show the best, median, and worst performances of the NONMEM three-compartment model when applied to the ten subjects in the study.

**Deconvolution Analysis.** Figure 5 shows the results of the deconvolution of the plasma concentrations over time with the drug input function (i.e., the infusion). The thick lines show the unit disposition functions predicted by the pharmacokinetic parameters shown in table 4. The figure points out the similarity between the three parametric representations of the disposition function. However, the NONMEM prediction of the disposition function overestimates the individual disposition functions predicted by deconvolution analysis after 60 min. Conversely, the TS estimate of the disposition function underestimates the disposition functions beyond 90 min, and there is a suggestion that it subsequently flattens excessively and over-predicts the

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disposition function after 120 min. The disposition function estimated by the NPD analysis is visually the best estimate of the central tendency of the disposition functions determined by individual deconvolution analysis.

Computer Simulations. The results of the computer simulations are shown in figure 6. The remifentanil simulation indicates that only a few minutes is necessary to achieve a 50% decrease in blood drug concentration despite very lengthy infusions. As the infusion duration lengthens, the remifentanil curve asymptotically approaches 3 min. This is in contrast to fentanyl, and to a lesser extent alfentanil and sufentanil, for which the time to achieve a decrease in blood concentration by 50% is much more prolonged and exhibits a marked dependence upon the infusion duration.

Discussion

This study has described the pharmacokinetics of remifentanil in terms of a nonparametric moment analysis, several parametric compartmental analyses, a deconvolution analysis, and a more intuitively meaningful computer simulation. Viewed from the perspective of all these analytical methods, the obviously striking feature of remifentanil's pharmacokinetics is the very rapid decay in remifentanil blood concentrations after termination of an infusion. Pharmacokinetically, with respect to the speed with which concentrations of the drug decrease in the blood, remifentanil represents a new pharmacokinetic class of opioid.

The complexities encountered in the modeling of remifentanil warrant discussion. Our data did not permit an entirely satisfying determination as to the number of compartments necessary for the population model. This is perhaps inevitable in early studies of new drugs in which only a small number of subjects are studied. With a constant term in the variance model, the two-compartment pharmacokinetic model accurately described the observations before approximately 60 min but consistently under-predicted the observations beyond that time. The constant term in the variance model allowed the nonlinear regression to ignore the very low concentrations that were poorly predicted by the two-compartment model. However, the two-compartment fit produced terminal half-life estimates of approximately 10 min, satisfying the occasionally stated requirement that the duration of sampling be 3–5 times the terminal half-life.

Table 5. Two-stage, Pooled, and 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>Two-stage</td>
<td>16.1</td>
<td>2.4</td>
<td>40.7</td>
</tr>
<tr>
<td>Pooled</td>
<td>15.6</td>
<td>2.2</td>
<td>35.2</td>
</tr>
<tr>
<td>NONMEM</td>
<td>14.8</td>
<td>2.6</td>
<td>35.2</td>
</tr>
</tbody>
</table>

MDAWR = median absolute weighted residual.

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Fig. 4. The best, median, and worst performances of the two-stage (TS), naive pooled data (NPD), and NONMEM three-compartment population models when applied to the individual data sets. The dots represent measured remifentanil concentrations; the solid lines represent the concentrations predicted by the population models.

Fig. 5. Deconvolution analysis of the individual data sets compared to the disposition functions of the TS, NPD, and NONMEM analysis. Each thin line represents a deconvolution of a single concentration versus time curve against the infusion input. The thicker lines represent the population disposition functions of the parametric, compartmental models. The inset in the upper right corner is an expanded view of the first 15 min.
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The three-compartment model, by contrast, produced imprecise estimates of the terminal half-life ranging from 48 min (NONMEM) to 170 min (TS). With sampling ranges from 120 to 150 min, we cannot be confident in any of these estimates of the terminal half-life, as suggested by the large coefficients of variation obtained from both the TS and the NONMEM analyses. However, this slower terminal phase clearly exists, and ignoring the terminal phase with a two-compartment model is less satisfactory because a substantial portion of the data are not well described. A more precise description of the slow terminal phase of remifentanil pharmacokinetics will require either development of a more sensitive assay or administration of larger doses of remifentanil than administered in this study. However, the context sensitive half-time of 3 min obtained from the computer simulation should not be affected by any change in the estimate of the terminal half-life because the fractional coefficient of this half-life is less than 0.1%. Thus, the slow terminal half-life is of negligible clinical relevance.

We used three different parametric analysis techniques (TS, NPD, and NONMEM) for two reasons. First, we wanted to characterize the pharmacokinetics as accurately as possible. Second, we wanted to compare two simple techniques, the TS and NPD approaches, with the more complex NONMEM analysis. Although we used MKMODEL for the TS and NPD techniques, these techniques are easily implemented on any spreadsheet with a "solver" function. By contrast, NONMEM is a complex program that requires a substantial commitment of time to install and learn. Interestingly, the volumes and clearances estimated by all three techniques were quite similar.

A better estimate of performance might be how well the predictions of the parametric disposition functions estimated by each technique predict the disposition functions calculated by numeric deconvolution for each subject. Figure 5 shows that the predictions of the three techniques are almost identical for the first 30 min. As the predictions diverge after 60 min, the predictions of the NPD technique are more similar to those of the NONMEM technique than are the predictions of the "standard" TS analysis. The TS curve appears to flatten inappropriately beyond 120 min, whereas the NONMEM curve appears to be inappropriately high throughout much of its course. By this measure, the parameters estimated by NONMEM and the TS technique provide a poorer estimate of the disposition functions in the individuals, whereas the parameters estimated by the NPD technique provide the best. Thus, if one is to choose a simple technique for analysis of pharmacokinetic data such as these, our results suggest the NPD technique should be considered, despite the unfortunate pejorative "naive" that has been used to describe the technique.

It has been suggested that pharmacokinetic parameters estimated using the TS and NPD approaches are biased compared with those estimated using more sophisticated population approaches. Our data do not support this conclusion. All three techniques provided similar estimates of the pharmacokinetics. Computational efficiency would favor the NPD approach. However, if the presence or absence of a sample in the study depends on the pharmacokinetics (e.g., samples are drawn when a certain drug effect is observed, unlike the present study, in which the sample times were determined in advance), then it is likely that pharmacokinetics predicted by the NPD technique would be biased, and we would suggest that either a TS or a population technique be used. Additionally, if the variance about the parameters is of interest, then the more complex NONMEM approach is justified.

Inspection of the simulation results is perhaps the best means of underscoring the unique pharmacokinetic profile of remifentanil. The simulations predict the time necessary to achieve a 50% decrease in drug concentration for remifentanil, fentanyl, alfentanil, and

Fig. 6. A simulation of the time necessary to achieve a 50% decrease in drug concentration in the blood (or plasma) after variable-length intravenous infusions of remifentanil, fentanyl, alfentanil, and sufentanil. The simulation for remifentanil was done using the NONMEM three-compartment model parameters; the curves for the other opioids were simulated using parameters obtained from the literature (see text).
sufentanil (fig. 6). Using the concepts developed by Shafer and Varvel, these simulations are an attempt to provide "context sensitive half times" as proposed by Hughes et al. In this case, the "context" is the duration of a continuous infusion. Such simulations are intended to provide more clinically relevant meaning to pharmacokinetic analysis. Based upon these simulations, remifentanil is unique compared to the currently available potent opioids, exhibiting a very short context-sensitive half-time that is independent of infusion duration.

It is important to emphasize that comparison of the terminal half-life of remifentanil with those of the other potent opioids is misleading because it does not accurately reflect the differences in the overall concentration decay curve. While the TS terminal half-life of remifentanil is similar to that of alfentanil, the overall decay of remifentanil concentrations in the blood is faster. This is because the terminal half-life of remifentanil is responsible for only a very small portion of the overall concentration decay, as evidenced by the third-compartment fractional coefficient of about 0.1% (table 4). Thus, although the terminal half-life contributes to the overall description of the data, it is not indicative of the differences between remifentanil and the other potent opioids in terms of the rapidity with which drug levels decrease. There is growing appreciation for the fact that terminal half-lives are not reflective of the overall concentration decay curve, and that they alone should not be the basis of clinical decisions regarding the expected duration of drug effect.

The implications of remifentanil's pharmacokinetic profile when applied to clinical anesthesia are clear. There has long been a definitive need for a very brief-acting opioid. Potential advantages of an ultra-short-acting opioid such as remifentanil could include: (1) the ability to rapidly decrease drug effect to an appropriate level intraoperatively, (2) a decreased likelihood of undesirable opioid side effects postoperatively (e.g., respiratory depression), (3) the lack of drug accumulation with repeated bolus injection or prolonged intravenous infusion, and (4) the absence of prolonged metabolism with hepatic or renal disease. Theoretical disadvantages include: (1) the necessity for administration by infusion techniques and (2) the lack of prolonged opioid effect when such effects are desirable (e.g., postoperative analgesia).

Despite these possible disadvantages, the clinical potential for remifentanil is promising. Studies describing the pharmacokinetics of remifentanil in various patient groups and disease states, the pharmacodynamics of the drug relative to other opioids, and its application in various clinical settings will define this new agent's place among the currently used opioids.

References

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