Population Pharmacokinetics of Alfentanil: The Average Dose–
Plasma Concentration Relationship and Interindividual
Variability in Patients

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Dick A. Thomson, M.D. Ph.D.,§ Donald R. Stanski, M.D.¶

The population pharmacokinetic parameters describing the plasma concentration versus time profile of alfentanil in patients undergoing general anesthesia were determined from 614 plasma concentration measurements collected in four previously reported studies with a total of 45 patients. A nonlinear regression analysis evaluating the effect of six concomitant variables revealed a significant influence of body weight on the volume of the central compartment ($V_c$) and a decrease with age of total body clearance (CL) and of redistribution rate from the deep compartment ($k_{d}$). A small but significant effect of sex on the $V_c$ was also observed. The duration of anesthesia and the concomitant administration of inhalational anesthetics had no effect on alfentanil pharmacokinetic parameters. The mean CL and $V_c$ for alfentanil in a 70-kg male, aged less than 40 yr, were estimated as 0.356 l/min and 7.77 l, respectively. After correction for age, body weight, and sex, the remaining interindividual variability of alfentanil kinetics (expressed as coefficient of variation) was 48% for CL and 35% for $V_c$. These population pharmacokinetic parameter estimates should increase the accuracy of predicting concentration–time profiles for intravenous alfentanil infusions. A computer program is presented that allows prediction of the alfentanil plasma concentration and the 68% confidence limits of the prediction from the study data analysis. (Key words: Analgesics: alfentanil. Anesthetics, intravenous: alfentanil. Pharmacokinetics: population.)

ALFENTANIL IS A NEW OPIATE WITH A UNIQUE PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE. COMPARED WITH FENTANYL, IT HAS A SHORT TERMINAL ELIMINATION HALF-LIFE BECAUSE OF THE RELATIVELY SMALL STEADY-STATE DISTRIBUTION VOLUME.1 ITS SHORT BLOOD-BRAIN EQUILIBRATION TIME RESULTS IN

**Abbreviations**

$A_1$, $A_2$, $A_3$, = hybrid rate constants characterizing a triexponential
$\lambda_1$, $\lambda_2$, $\lambda_3$, = decay function (min$^{-1}$)

BW = body weight (kg)

CL = total body clearance (l/min)

CL$_j$ = true unknown clearance of patient j

$CL_{e}$ = estimated clearance of patient j

$CL_{av}$ = mean value of clearance in patients $\leq$ 40 yr (l/min)

$C_p$ = concentration at any time t (µg/l)

$C_{pb}$ = concentration producing a clinically measurable effect in 50% of patients

$k_{el}$ = elimination rate constant from compartment 1 (min$^{-1}$)

$k_{12}$ = rate constant for drug transfer from compartment 1 to compartment 2 (min$^{-1}$)

$k_{13}$ = rate constant for drug transfer from compartment 1 to compartment 3 (min$^{-1}$)

$k_{21}$ = rate constant for drug transfer from compartment 2 to compartment 1 (min$^{-1}$)

$k_{31}$ = rate constant for drug transfer from compartment 3 to compartment 1 (min$^{-1}$)

$k_{51}$ = estimated $k_{51}$ of patient j

$k_{51}$ = mean value of $k_{51}$ in patients $\leq$ 40 yr (min$^{-1}$)

LLD = log likelihood difference (difference in the value of twice the log likelihood function, i.e., twice the log

$\lambda$ = any specified time following start of the infusion or

iv administration (min)

$V_c$ = volume of central compartment (l)

$\bar{V}_c$ = population mean value of the volume of the central compartment (l)

$\bar{V}_{c,av}$ = population mean value of the weight-normalized volume of the central compartment (l/kg)

$\omega_{c,av}$ = interindividual variance of CL

$\omega_{V_c,av}$ = interindividual variance of $V_c$

$\sigma^2$ = residual intrapatient variance

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TABLE 1. Characteristics of the Five Study Groups from which the Data Were Taken

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Investigator</th>
<th>Patient and Type of Surgery</th>
<th>Induction of Anesthesia</th>
<th>Concomitant Administration of Inhalational Anesthetics</th>
<th>Body Weight (kg) Mean (range)</th>
<th>No. of Patients</th>
<th>Age (yr) Mean (range)</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boivin12</td>
<td>Middle-aged adults: various surgical procedures</td>
<td>Thiopental</td>
<td>Yes</td>
<td>71.1 (52-79)</td>
<td>11</td>
<td>44.2 (19-63)</td>
<td>RIA</td>
</tr>
<tr>
<td>2</td>
<td>Camu13</td>
<td>Middle-aged women: general surgery</td>
<td>Etomidate</td>
<td>Yes</td>
<td>57.3 (46-72)</td>
<td>5</td>
<td>43.0 (35-55)</td>
<td>GLC</td>
</tr>
<tr>
<td>3</td>
<td>Helmers14</td>
<td>Middle-aged adults: abdominal surgery</td>
<td>Etomidate</td>
<td>Yes</td>
<td>69.6 (54-102)</td>
<td>9</td>
<td>35.9 (27-44)</td>
<td>RIA</td>
</tr>
<tr>
<td>4</td>
<td>Helmers14</td>
<td>Elderly patients: abdominal surgery</td>
<td>Etomidate</td>
<td>Yes</td>
<td>66.3 (46-81)</td>
<td>15</td>
<td>76.3 (68-91)</td>
<td>RIA</td>
</tr>
<tr>
<td>5</td>
<td>Schüttler15</td>
<td>Middle-aged women: short gynecologic surgery</td>
<td>Thiopental</td>
<td>No</td>
<td>61.3 (51-70)</td>
<td>5</td>
<td>37.0 (24-44)</td>
<td>RIA</td>
</tr>
</tbody>
</table>

RIA = radioimmunoassay; GLC = gas liquid chromatography.

a rapid onset of narcotic effect (peak effect occurs in 1–2 min). Because of this short blood-brain equilibration, redistribution of the drug from the brain to other tissues is an important factor in the dissipation of alfentanil's narcotic effect after bolus intravenous administration. A continuous infusion of alfentanil is necessary to maintain adequate plasma concentrations and narcotic effect for longer surgical procedures (i.e., greater than 30 min). Recently, the therapeutic plasma concentrations of alfentanil have been defined for perioperative events. Different surgical/anesthesia stimuli require different alfentanil plasma concentrations to provide adequate clinical anesthesia. To ablate the hemodynamic responses to upper abdominal surgery, an average alfentanil plasma concentration of 412 ng/ml was needed, while adequate postoperative spontaneous respiration required an average alfentanil plasma concentration below 223 ng/ml. Ausems and Hug have shown that a variable-rate alfentanil infusion can be used effectively to change the alfentanil plasma concentrations required for changing surgical stimuli.

Given that the therapeutic plasma concentrations of alfentanil are known, it is possible to use pharmacokinetic concepts (the mathematical relationship between dose and plasma concentration) to design drug-administration schemes for the infusion of alfentanil. A two- or three-infusion rate scheme has been proposed and evaluated in achieving steady-state alfentanil plasma concentrations. Recently, a computer-driven infusion pump that uses a pharmacokinetic model of alfentanil disposition has been used to rapidly achieve and maintain the desired alfentanil plasma concentrations during a surgical procedure. All of these dosing concepts require the appropriate alfentanil pharmacokinetic data. In any population of patients, pharmacokinetic parameters that describe the average patient can be derived. It is obvious that identical infusion rates in different patients will result in different alfentanil plasma concentrations. The variability that occurs between patients (interindividual) and within a patient (intraindividual) causes the average pharmacokinetic data to achieve different plasma concentrations in each patient. A major goal of pharmacokinetic research is to identify those factors that may significantly alter a drug's pharmacokinetics (i.e., age, weight, disease states, other drugs) and to adjust appropriately the dosing scheme. A second goal is to quantitate the degree of interindividual and intraindividual pharmacokinetic variability in the population. With this information, one can predict the average concentration and the confidence bounds for a given drug administration scheme.

The goal of this study was to determine the alfentanil population (average) pharmacokinetic parameters and the interindividual and intraindividual variability of the population pharmacokinetics. For this purpose, published alfentanil plasma concentration data obtained by four different investigators from patients receiving general anesthesia were analyzed. The effect of six selected variables (age, weight, sex, induction agent, use of an inhalational anesthetic, and duration of anesthesia) on alfentanil pharmacokinetics was also evaluated.

Methods

Patients

Data from four previously published studies were pooled. They consist of five study groups (table 1) with a total of 45 patients and 614 alfentanil plasma concentrations. In all patients, alfentanil was administered at the beginning of anesthesia, either as an intravenous bolus or as a short infusion over 10–30 s. The doses ranged between 50 and 120 µg/kg. The plasma concentration profile was followed during 4–12 hr after administration. In addition to the time of sampling and the plasma concen-
tion value, the data collected in each individual included the following six variables: age, body weight, sex, duration of anesthesia, concomitant administration of etomidate and/or inhalational anesthetics. Table 1 summarizes the distribution of these characteristics in the five different study groups. Figure 1 shows the plot of the 45 dose-normalized plasma concentration profiles. The details of the intraoperative patient management are indicated in the original publications.

**Assay**

Plasma alfentanil concentrations were measured using a radioimmunoassay (RIA) method for Groups 1, 3, 4, and 5 and a gas liquid chromatography (GLC) method for Group 2. The RIA was performed according to the classical procedure, i.e., the antiserum was added last to the mixture of unknown sample and $^3$H-alfentanil. A comparison of the RIA and GLC methods revealed a close agreement without any systematic differences (Woestenborghs and Heykants, unpublished results).

**Data Analysis**

The NONMEM program, developed for population pharmacokinetic analysis by Beal and Sheiner, was used to analyze the plasma concentration data. The method has been described previously in detail. It implements a multiple nonlinear regression procedure to derive the population average of the pharmacokinetic parameters and to identify the factors that may influence them. One of the most important features of NONMEM as compared with standard nonlinear regression programs applied to pharmacokinetics, e.g., NONLIN, is its ability to pool simultaneously data from different patients. This has several advantages: 1) the number of samples per individual can be kept relatively small; 2) the influence of concomitant variables on the pharmacokinetic parameters can be directly investigated; and 3) the residual interindividual variability of the pharmacokinetic parameters can be estimated in addition to their mean values. In this way, it is possible to describe the average pharmacokinetic profile of a drug in a patient population and also to estimate the magnitude of the differences in the plasma concentration expected under a given dosage in different patients.

**Pharmacokinetic Model**

A three-compartment open body model with elimination from the central compartment was assumed (fig. 2). The pharmacokinetic model assumed that alfentanil pharmacokinetics are first order and concentration independent. Preliminary analysis comparing three- and two-compartment models unequivocally favored the former (see "Results"). Because one of the major goals of this study was to determine the effect of different patient characteristics and interventions on the basic model parameters, in particular on the total body clearance and the volume of distribution of the central compartment, the following parameterization was chosen: volume of distribution of the central compartment ($V_c$), total body clearance (CL), and the microconstants ($k_{12}$, $k_{21}$, $k_{13}$, $k_{31}$). The closed-form solution for the plasma concentration at time "t" can be written as a sum of three exponentials:

$$C_p(t) = A_1e^{-\lambda_1t} + A_2e^{-\lambda_2t} + A_3e^{-\lambda_3t} \quad (1)$$

where $A_1$, $A_2$, $A_3$, $\lambda_1$, $\lambda_2$, and $\lambda_3$ are hybrid functions of the six parameters just mentioned. The values of CL, $V_c$, $k_{12}$, $k_{21}$, $k_{13}$, and $k_{31}$ are estimated by the nonlinear

**Figure 2. A three-compartment model.**
regression program. The calculation of \( \lambda_1, \lambda_2, \lambda_3 \) and \( \Lambda_1, \Lambda_2, \Lambda_3 \) from these six parameters and the partial derivatives of the plasma concentration with respect to each parameter, required by NONMEM, were performed by a subroutine written in FORTRAN.

In order to investigate the influence of age, weight, sex, duration of anesthesia, and inhalational anesthetics on the pharmacokinetics of alfentanil, additional regression parameters (termed influencing parameters) were included in the model quantifying the relationship between these factors and the pharmacokinetic parameters. For example, the effect of age on CL for patients more than 40 yr old was found to be best described by the following relationship:

\[
\widehat{\text{CL}}_j = \overline{\text{CL}}_\gamma - F_{\text{age}} \cdot (\text{Age}_j - 40)
\]  

where \( \overline{\text{CL}}_\gamma \) is the estimate of the mean population value for patients less than 40 years old; \( \widehat{\text{CL}}_j \) is the estimate of the clearance value of patient \( j \) corrected for his or her age; and \( F_{\text{age}} \) is an influencing parameter, the value of which is estimated by NONMEM during the regression.

**INTERINDIVIDUAL VARIABILITY**

Although a part of the interindividual variability of alfentanil pharmacokinetics can be explained by the factors mentioned earlier, there will always remain some difference in the plasma-concentration profile among patients. To both describe this unexplained interindividual variability and estimate its magnitude, random effects are included in the regression model that allow some parameters to vary (randomly) among patients. A log normal distribution was assumed to describe the interindividual variability of the pharmacokinetic parameters. This choice was based on our own previous experience and other published reports, which showed that in most cases, a log-normal (skewed) distribution, rather than a normal distribution, better approximates the frequency distribution of the pharmacokinetic parameters in a patient population. An example of a log-normal distribution, derived in this study, of the CL of alfentanil is shown in figure 3. To express this in the regression model, log-additive random interindividual error is assumed. Thus, for CL we can write:

\[
\ln \text{CL}_j = \ln \widehat{\text{CL}}_j + \eta_j \text{CL}
\]

or

\[
\text{CL}_j = \widehat{\text{CL}}_j \cdot e^{\eta_j \text{CL}}
\]

where \( \eta_j \text{CL} \) is a random variable with mean value zero and variance \( \omega^2_{\text{CL}} \). Note that \( \omega^2_{\text{CL}} \) is also the interindividual variance of CL after correcting for age. Similarly for \( V_e \):

\[
\ln V_e = \ln \widehat{V}_e + \eta_{V_e}
\]

where \( \eta_{V_e} \) is a random variable with mean zero and variance \( \omega^2_{V_e} \).

A log-additive model was also assumed for the remaining unexplained intrindividual variability, which is due to assay errors, time recording inaccuracy, model misspecification, or changes in the patient's physiologic state during the sampling period:

\[
\ln C_{p_j} = \ln \widehat{C}_{p_j} + \epsilon_j
\]

where \( C_{p_j} \) is the "i"th measured plasma concentration in the "j"th individual, \( \widehat{C}_{p_j} \) is the corresponding predicted concentration (Equation 1), and \( \epsilon_j \) is a random variable with mean zero and variance \( \sigma^2 \). By using a log-additive model for the residual error, one states that the error between the observed and the predicted concentrations increases approximately in proportion to the predicted concentration, a phenomenon frequently observed with pharmacokinetic data. In addition, the model assumes that the variances of \( \eta \) and \( \epsilon \) are the same in the different study groups.

**REGRESSION PROCEDURE AND GOODNESS OF FIT TEST**

A modified stepwise procedure, analogous to multiple stepwise linear regression analysis, was used to deter-
TABLE 2. Regression Analysis: Two- versus Three-compartment Model

<table>
<thead>
<tr>
<th>Model</th>
<th>$\overline{CL}$ (l/min)</th>
<th>$V_r$ (l)</th>
<th>$k_{a1}$ (min$^{-1}$)</th>
<th>$k_{a2}$ (min$^{-1}$)</th>
<th>$k_{s1}$ (min$^{-1}$)</th>
<th>$k_{s2}$ (min$^{-1}$)</th>
<th>$k_{s3}$ (min$^{-1}$)</th>
<th>LLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-compartment model</td>
<td>0.276</td>
<td>10.1</td>
<td>0.0699</td>
<td>0.0224</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Three-compartment model</td>
<td>0.278</td>
<td>7.85</td>
<td>0.117</td>
<td>0.0775</td>
<td>0.0221</td>
<td>0.00997</td>
<td>142*</td>
<td></td>
</tr>
</tbody>
</table>

* $P < 0.0005$.

mine which influencing parameters should be included in the final model describing the population pharmacokinetics of alfentanil. At each step the results of two computer runs were compared. In one, the parameter in question is free to be estimated; in the second, it is constrained to a hypothesized value, which corresponds to the null hypothesis (i.e., no effect of the influencing parameter). The following decision criteria were considered when choosing between the two models: the difference in −2 log likelihood (LLD), which is supplied by NONMEM (asymptotically $x^2$ distributed, analogous to F-value in linear regression), the standard errors and correlation matrix of the parameter estimates, the residual plots, and the change in the remaining random interindividual variability. Because of the asymptotic nature of the $x^2$ test, a conservative value of 7.8 for the LLD (corresponding to $P < 0.005$ for 1 degree of freedom) was chosen as the minimum value at which a parameter could be included in the final regression model.

The nonlinear regression analysis was divided into six parts:

1. The original data file, containing 614 plasma concentration measurements, was randomly divided into two subsets containing all individuals but only one-half of the plasma concentration measurements. Only the first subset, comprising 307 data points, was then used for the subsequent regression analysis (parts 2–5).

2. The fixed effects (the pharmacokinetic parameters and their influencing factors) were evaluated using a modified forward stepwise procedure as described earlier.

3. For each parameter that remained in the model at the end of part 2, its contribution was reevaluated when all other parameters were included in the regression model.

4. The random effects (the variance components) were evaluated with the best model found for the fixed effects in parts 2 and 3.

5. The fixed effects were again reevaluated, as in part 3, with the final model for random effects.

6. Finally, the goodness of fit was tested with the second half of the data not used in parts 2–5. This data subset was fitted to the final regression model with all parameters constrained to their estimated values, and the variance of the residual (intraindividual error ($\sigma^2$)) was determined. A good fit should result in similar estimates of $\sigma^2$ with both data subsets.

Results

The results at different steps of the regression analysis that yielded significant differences between the two models are described in tables 2–7.

NUMBER OF COMPARTMENTS

The comparison of two- and three-compartment models is shown in table 2. It can be seen that the data could be better described by the three-compartment model ($P < 0.0005$).

AGE

Retaining the three-compartment model, the effect of age on alfentanil pharmacokinetics was then studied. Out
Table 4. Regression Analysis: Effect of Body Weight on $V_c$

<table>
<thead>
<tr>
<th>Parameter Model</th>
<th>$\bar{CL}$ (l/min)</th>
<th>$\bar{V}_c$ (l/kg)</th>
<th>$k_{12}$ (min⁻¹)</th>
<th>$k_{31}$ (min⁻¹)</th>
<th>$F_{a\alpha}$</th>
<th>$F_{m\alpha}$</th>
<th>LLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_c$ independent of BW</td>
<td>0.333</td>
<td>8.01 (l)</td>
<td>0.110</td>
<td>0.0554</td>
<td>0.00965</td>
<td>0.00762</td>
<td>0.00264</td>
</tr>
<tr>
<td>$V_c$ expressed per kgBW</td>
<td>0.371</td>
<td>0.127 (l/kg)</td>
<td>0.108</td>
<td>0.0707</td>
<td>0.0182</td>
<td>0.0131</td>
<td>0.00245</td>
</tr>
</tbody>
</table>

* $P < 0.0005.$

† $F_{a\alpha}$ and $F_{m\alpha}$ = 0 for Age $\leq$ 40 yr.

Table 5. Regression Analysis: Effect of Sex on $V_c$

<table>
<thead>
<tr>
<th>Parameter Model</th>
<th>$\bar{CL}$ (l/min)</th>
<th>$\bar{V}_c$ (l/kg)</th>
<th>$k_{12}$ (min⁻¹)</th>
<th>$k_{31}$ (min⁻¹)</th>
<th>$F_{a\alpha}$</th>
<th>$F_{m\alpha}$</th>
<th>LLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No influence of sex</td>
<td>0.371</td>
<td>0.127</td>
<td>0.108</td>
<td>0.0707</td>
<td>0.0182</td>
<td>0.0131</td>
<td>0.00245</td>
</tr>
<tr>
<td>Vc corrected for sex</td>
<td>0.356</td>
<td>0.111</td>
<td>0.102</td>
<td>0.0673</td>
<td>0.0170</td>
<td>0.0126</td>
<td>0.00267</td>
</tr>
</tbody>
</table>

* $P < 0.0005.$

† $F_{a\alpha}$ and $F_{m\alpha}$ = 0 for Age $\leq$ 40 yr.

of the six pharmacokinetic parameters, a significant association with age was found for $CL$ and $k_{31}$ (table 3). The influence of age could be best described by the following relationship:

1) No influence of age for patients 40 yr and younger;
2) A linearly decreasing function of age for patients more than 40 yr old:

$$\bar{CL}_j = \bar{CL}_y - F_{CL} \cdot (Age_j - 40)$$  \hspace{1cm} (7)

Table 6. Estimates of Fixed Effects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NONMEM Estimates (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CL$ (l/min)</td>
<td>Age $\leq$ 40</td>
</tr>
<tr>
<td>$CL$ (l/min)</td>
<td>Age $&gt; 40$</td>
</tr>
<tr>
<td>$k_{12}$ (min⁻¹)</td>
<td></td>
</tr>
<tr>
<td>$k_{31}$ (min⁻¹)</td>
<td></td>
</tr>
<tr>
<td>$k_{31}$ (min⁻¹)</td>
<td>Age $\leq$ 40</td>
</tr>
<tr>
<td>$k_{31}$ (min⁻¹)</td>
<td>Age $&gt; 40$</td>
</tr>
<tr>
<td>$V_c$ (l/kg)</td>
<td>Male</td>
</tr>
<tr>
<td>$V_c$ (l/kg)</td>
<td>Female</td>
</tr>
</tbody>
</table>

Table 7. Estimates of Random Effects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NONMEM Estimates* (±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interindividual variability of $CL$†</td>
<td>48% (±9)</td>
</tr>
<tr>
<td>Interindividual variability of $V_c$†</td>
<td>33% (±6)</td>
</tr>
<tr>
<td>Residual intrindividual variability</td>
<td>25% (±2)</td>
</tr>
</tbody>
</table>

* Expressed as coefficient of variation.
† A positive correlation between $CL$ and $V_c$ was found ($r = 0.46$).

and

$$\hat{k}_{31j} = \bar{k}_{31y} - F_{k31j} \cdot (Age_j - 40)$$  \hspace{1cm} (8)

where $\bar{CL}_j$ and $\bar{k}_{31y}$ are corrected estimates for patient $j$ aged $Age_j$; $\bar{CL}_y$ and $\bar{k}_{31y}$ are mean population values for young patients ($\leq 40$ yr); and $F_{CL}$ and $F_{k31}$ are the slopes of the linear relationship between age and the pharmacokinetic parameters (see also Abbreviations for definition of symbols).

Thus, the model implies that $CL$ and $k_{31}$ remain constant up to 40 yr and then linearly decrease as a function of age. This relationship was found to describe best the difference between old and young and was empirically derived by comparing several models.

Body Weight

Retaining the effect of age on both $CL$ and $k_{31}$, the influence of body weight was then investigated. No relationship between body weight and the $CL$ of alfentanil was found, but normalization of $V_c$ for body weight yielded a definite improvement of the fit. The influence of body weight on $V_c$ can be described as follows:

$$\hat{V}_c = \hat{V}_{c0} \cdot BW_j$$  \hspace{1cm} (9)

where $\hat{V}_c$ defines the estimate of the central compartment volume (in l) of patient $j$. $BW_j$ is the body weight in kg, and $\hat{V}_{c0}$ is the population mean of the weight-normalized volume of the central compartment (in l/kg). Table 4 shows the results obtained without and with the inclusion of individual body weight in the regression model.
We also tested a model correcting the \( V_e \) by body weight raised to a power different from 1 (i.e., \( \hat{\bar{V}}_e = \bar{V}_e \cdot BW^j \)), but no improvement of the prediction of \( V_e \) was achieved by including this additional parameter.

**SEX**

A small but consistent effect of sex on \( V_e \) was found. The volume of distribution (normalized for body weight) was 15% larger in females compared to males (table 5). Thus:

\[
\hat{\bar{V}}_e = \bar{V}_e \cdot BW_j \cdot F_{sex}
\]

where \( F_{sex} \) represents the effect of sex on \( V_e \) for female patients and is constrained to 1.0 for males.

**OTHER CONCOMITANT VARIABLES**

The following factors were not retained in the regression model: duration of anesthesia, administration of etomidate for induction, and use of inhalational anesthetics. Inhalational anesthetics and the duration of anesthesia clearly lacked a significant influence on alfentanil pharmacokinetics (LLD < 5), but the influence of etomidate was questionable. Expressing CL, \( V_e \), and \( k_{12} \) as a function of etomidate administration resulted in relatively large differences in the \( -2 \log \) likelihood criterion. However, a large standard error of the estimates of magnitude of these effects and a high correlation with other influencing parameters, in particular with age, did not allow a definite conclusion concerning this drug interaction. This was probably due to an uneven distribution of this factor among the different study groups (table 1). For these reasons, the influence of etomidate was not retained in the regression model. We believe, however, that the question of the pharmacokinetic interaction between etomidate and alfentanil deserves further study.

**VARIABILITY OF ALFENTANIL KINETICS**

The unexplained interindividual differences in the plasma concentration profile of alfentanil could be described by a relatively simple random-effect model assigning interindividual variability to only two pharmacokinetic parameters: the CL and the volume of distribution of the central compartment. The interindividual (unexplained) variability was found for CL to be 48% (coefficient of variation) and for \( V_e \) 33%. A significant correlation between CL and \( V_e \) was present across patients (\( r = 0.46 \)). The residual intraindividual variability was estimated as 25% (coefficient of variation). An example of the estimated probability density function (PDF) for CL is shown in figure 3.

**GOODNESS OF FIT**

To evaluate the goodness of fit of the final regression model, the second half of the data, not used during the stepwise regression analysis, was analyzed with all parameters constrained to their estimated values except the residual variance. The estimate of the residual variability using this new data set was close to the value determined from the original regression (20% vs. 24%, coefficient of variation), indicating adequate fit of the model to the concentration–time data in this patient population.

Tables 6 and 7 list the final estimates of all parameters, including the effect of age, body weight, and sex, and the interindividual and intraindividual variability based on the total of 614 plasma concentration measurements.

**Discussion**

Our data set consisted of most data previously published concerning alfentanil pharmacokinetics. Data from five groups of patients studied by Bovill et al.,12 Camu et al.,13 Helmers et al. (two groups),14 and Schüttler and Stoeckel15 were pooled. Two of these investigators used a two-compartment model to describe the pharmacokinetics of alfentanil and therefore are not directly comparable with our results. In particular, one would expect on the average an overestimation of both clearance and the volume of the central compartment if data obeying three-compartment pharmacokinetics are analyzed by a two-compartment model. This is probably the main reason why the CL of young patients (\( %40 \) yr) of the four just mentioned studies12–15 is, on average, higher than the value found in our analysis (0.461 vs. 0.356 l/min). However, the two studies that used a three-compartment model12,15 also report a clearance value approximately 30% higher than the value found in our study. The higher average CL found by Bovill et al.12 can be explained by two patients with an extremely high CL (0.820 and 1.323 l/min, i.e., almost two and three times the average value of their group). The influence of these two extreme values was much smaller when analyzing the whole set of 45 patients in our study. Both CL and \( V_e \) were found to be considerably higher by Camu et al.13 This was also noted during our analysis. As we could find no reason that would explain this difference, the data were not excluded from our analysis so as not to underestimate the interindividual variability of the pharmacokinetics of alfentanil in patients treated in different institutions.

We found age had a significant influence, as did Helmers et al.,14 who compared the alfentanil clearance in old and young adult patients. The magnitude of the influence of age also shows a good agreement (−30% in the study of Helmers et al. vs. −28% in the present study for a mean age of 77 yr). Our results thus confirm the findings
of these investigators in a larger context of all other studies. In contrast to Helmers et al.,14 we also found an influence of age on the intercompartamental clearance, indicating that the drug has a slower redistribution from the deep compartment in older patients. Again, because different models were used (two- vs. three-compartment models), no direct comparison is possible.

Although there was a significant and consistent effect of sex on the volume of the central compartment, the magnitude was small, 15%, and the practical relevance is probably not very important.

No relationship between body weight and the CL was found for alfentanil. Similar findings have been reported for other drugs.27 However, a normalization of $V_c$ for body weight yielded a definite improvement of the fit and a reduction of the interindividual variability.

The influence of age and body weight on alfentanil pharmacokinetics has direct practical implications: to achieve a desired steady-state concentration, the loading dose of alfentanil should be adjusted according to body weight; and the maintenance infusion rate does not have to be weight adjusted because clearance was not found to be related to body weight in the range of weights studied (46–102 kg), but it has to be reduced with increasing age. In addition, changes in drug distribution and elimination will influence the terminal half-life ($t_{1/2}$) of alfentanil. Older individuals with a greater body weight are expected to have longer $t_{1/2}$. For example, a young female patient with a body weight of 65 kg, a $t_{1/2}$ of 95 min can be calculated. In contrast, a 90-kg woman, 80 yr old, is expected to have a $t_{1/2}$ more than twice as long (201 min). This large difference shows the practical importance of the influence of age and body weight on alfentanil pharmacokinetics as found in this study. For calculation of $t_{1/2}$ from the basic parameters reported in tables 6 and 7, see appendix 1.

Probably the most important result of this study is the quantification of the residual unexplained interindividual variability of alfentanil pharmacokinetics. Indeed, just knowing the fixed effects (the pharmacokinetic parameters and their influencing factors) allows a prediction of the alfentanil concentration–time course to be made for each patient according to age, body weight, and sex. But this calculation yields only the “average” concentration curve from which individual patients may differ substantially. Only the additional knowledge of the random effects (the variance components) permit one to estimate how large these interindividual differences in the actually achieved concentration are expected to be, or in other words, how confident one can be about the predicted concentration. In practice this is accomplished by calculating the approximate 68% (i.e., mean ± 1 SD) or 95% (i.e., mean ± 2 SD) confidence interval of the predicted concentration, as illustrated by the following example.

Assume we wish to anesthetize, with alfentanil and $N_2O/O_2$, a 70-yr-old female weighing 48 kg for breast surgery. Her pharmacokinetic parameters for alfentanil and their interindividual variability can be derived from tables 6 and 7. Using the information about $C_{P_{90}}$ for various stages of anesthesia,4,5 we can now propose a dosing scheme, calculate the confidence interval for the plasma concentration versus time course, and compare it with the pharmacodynamic data. The calculation of the expected plasma concentration ± SD (approximate 68% confidence interval) can be easily performed on an average size microcomputer using the algorithm described in appendix 1. If the desired target concentration at a given time does not lie within the calculated confidence limits, the dosing scheme is modified. By “trial and error” a dosing strategy can be found such that the lower confidence limit is above the “$C_{P_{90}}$ for laryngoscopy” after the loading dose and above the “$C_{P_{90}}$ for skin incision” at the time the surgeon starts the noxious stimulation (fig. 4). To assume rapid recovery, the upper confidence limit should lie below the “$C_{P_{90}}$ for spontaneous respiration” at the end of the surgery. This is accomplished in our example by stopping the infusion 30 min before the completion of the surgical procedure (fig. 4).

This example illustrates the importance of taking interindividual pharmacokinetic variability into consideration when designing the optimal dosing scheme. The value of the population pharmacokinetic-analysis approach that was implemented in this study lies in its ability to provide
quantitative estimates of the magnitude of the interindividual variability, based on representative plasma concentration data. This allows the physician to assess the accuracy of a concentration prediction and the extent that it is limited by the interindividual variability. As can be seen from figure 4, even after correcting the pharmacokinetic parameters according to age, body weight, and sex, the interindividual variability of alfentanil plasma concentration remains relatively large. This large remaining unexplained pharmacokinetic variability indicates that additional plasma concentration measurements obtained intraoperatively as individual feedback information should be considered for optimal intravenous alfentanil anesthesia. Feedback control methods using drug level measurements have been successfully applied to other drugs. However, the implementation for alfentanil would, in addition to population pharmacokinetics derived in this study, require a rapid and reliable drug assay and computer software for efficient use of the individual feedback. The ideal method of individualizing alfentanil administration would be a continuous, noninvasive measure of the degree of narcotic effect on the brain. Thus, one would examine the drug effect instead of the pharmacokinetics, which are the driving force for the drug effect. Unfortunately, such a measure is not yet available, although the EEG power spectral analysis is being investigated.

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References
