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

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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_{31}). 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 33% 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% interval limits of the prediction from the study data analysis. (Key words: Analgesics: alfentanil. Anesthetics, intravenous: alfentanil. Pharmacokinetics: population.)

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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[31]

- $A_1, A_2, A_3, \lambda_1, \lambda_2, \lambda_3$ = hybrid rate constants characterizing a triexponential decay function (min^{-1})
- BW = body weight (kg)
- CL = total body clearance (l/min)
- CL_j = true unknown clearance of patient j
- $\widehat{CL}_j$ = estimated clearance of patient j
- $\overline{CL}_y$ = mean value of clearance in patients ≦ 40 yr (l/min)
- Cp = concentration at any time t (μg/l)
- Cp_{50} = concentration producing a clinically measurable effect in 50% of patients
- k_{10} = 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})
- $\hat{k}_{31_j}$ = estimated k_{31} of patient j
- $\bar{k}_{31_y}$ = mean value of k_{31} in patients ≦ 40 yr (min^{-1})
- LLD = log likelihood difference (difference in the value of twice the log likelihood function, *i.e.*, twice the log of the likelihood ratio)
- t = any specified time following start of the infusion or iv administration (min)
- V_c = volume of central compartment (l)
- $\overline{V}_c$ = population mean value of the volume of the central compartment (l)
- $\hat{V}_{c_j}$ = estimated volume of the central compartment of patient j
- $\overline{V}_{c_w}$ = population mean value of the weight-normalized volume of the central compartment (l/kg)
- ω^2_{CL} = interindividual variance of CL
- $\omega_{V_c}{}^2$ = interindividual variance of V_c
- σ^2 = residual intraindividual variance

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

Group No.	Investigator	Patient and Type of Surgery	Induction of Anesthesia	Concomitant Administration of Inhalational Anesthetics	Body Weight (kg) Mean (range)	No. of Patients	Age (yr) Mean (range)	Assay
1	Bovill[12]	Middle-aged adults: various surgical procedures	Thiopental	Yes	71.1 (52–79)	11	44.2 (19–63)	RIA
2	Camu[13]	Middle-aged women: general surgery	Etomidate	Yes	57.3 (46–72)	5	43.0 (33–55)	GLC
3	Helmers[14]	Middle-aged adults: abdominal surgery	Etomidate	Yes	69.6 (54–102)	9	35.9 (27–44)	RIA
4	Helmers[14]	Elderly patients: abdominal surgery	Etomidate	Yes	66.3 (46–81)	15	76.3 (68–91)	RIA
5	Schüttler[15]	Middle-aged women: short gynecologic surgery	Thiopental	No	61.3 (51–70)	5	37.0 (24–44)	RIA

RIA = radioimmunoassay; GLC = gas liquid chromatography.

a rapid onset of narcotic effect (peak effect occurs in 1–2 min).[2] 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).[3] Recently, the therapeutic plasma concentrations of alfentanil have been defined for perioperative events.[4,5] 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.[5] Ausems and Hug[4] 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[6,7] (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.[8] 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.[9,10] 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.[11] 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[12–15] 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[12–15] 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-

tration 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[16] (RIA) method for Groups 1, 3, 4, and 5 and a gas liquid chromatography[17] (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.[18] 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.[19] 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,[20] 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[21]:

$$Cp(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3e^{-\lambda_3 t} \quad (1)$$

where A_1, A_2, A_3, λ_1, λ_2, and λ_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

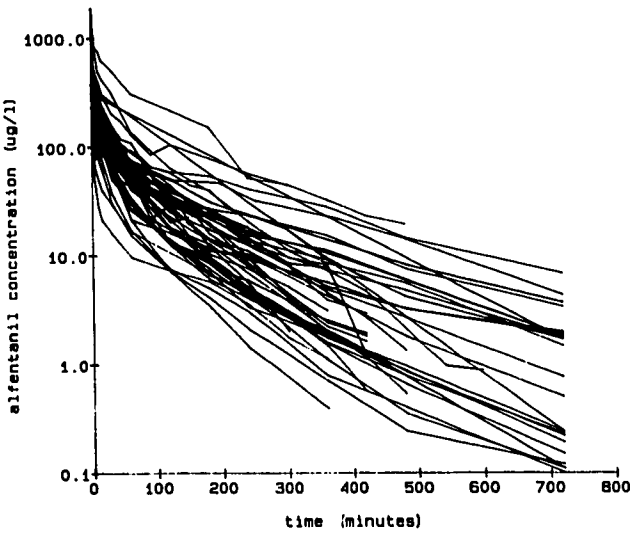

FIG. 1. Plot of the 45 alfentanil plasma concentration profiles. (Each concentration has been normalized for an iv bolus of 50 μg/kg for this figure only.)

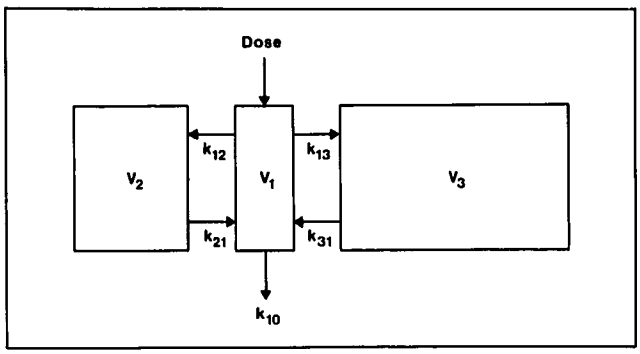

FIG. 2. A three-compartment model.

** Beal SL, Sheiner LB: NONMEM Users Guide. San Francisco, University of California, 1979.

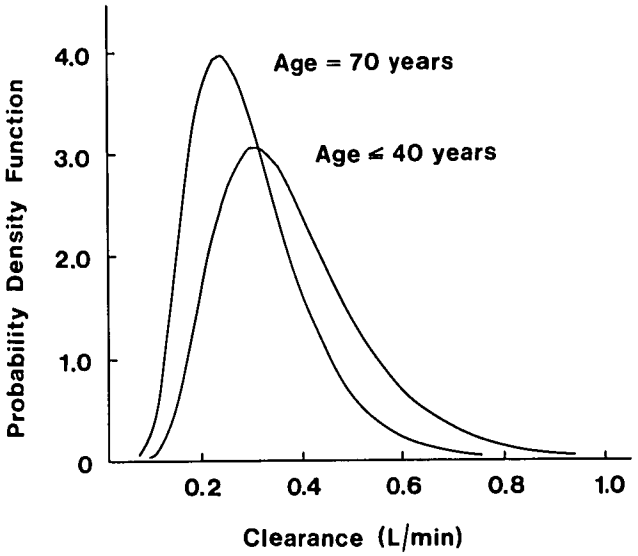

FIG. 3. Estimated probability density function (PDF) for the total body clearance of alfentanil in the patient populations aged 40 or less and 70 yr, respectively. Log-normal distribution is assumed. (PDF of a random variable, *i.e.*, clearance in this example, defines the probability that the random variable will assume a value within a given interval. The PDF of a log-normal distribution is characterized by the mean and the standard deviation, which are estimated by NONMEM.)

regression program. The calculation of λ_1, λ_2, λ_3 and A_1, A_2, A_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 etomidate 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:

$$\widehat{CL}_j = \overline{CL}_y - F_{age} \cdot (Age_j - 40) \quad (2)$$

where $\overline{CL}_y$ is the estimate of the mean population value for patients less than 40 years old; $\widehat{CL}_j$ is the estimate of the clearance value of patient j corrected for his or her age; and F_{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 m del 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.[22-25] 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:

$$\ln CL_j = \ln \widehat{CL}_j + \eta_{jCL} \quad (3)$$

or

$$CL_j = \widehat{CL}_j \cdot e^{\eta_{jCL}} \quad (4)$$

where η_{jCL} is a random variable with mean value zero and variance ω^2_{CL}. Note that ω^2_{CL} is also the interindividual variance of CL after correcting for age. Similarly for V_c:

$$\ln V_{c_j} = \ln \widehat{V}_{c_j} + \eta_{jV_c} \quad (5)$$

where η_{jV_c} is a random variable with mean zero and variance $\omega^2_{V_c}$.

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

$$\ln Cp_{ij} = \ln \widehat{Cp}_{ij} + \epsilon_{ij} \quad (6)$$

where Cp_{ij} is the "i"th measured plasma concentration in the "j"th individual, $\widehat{Cp}_{ij}$ is the corresponding predicted concentration (Equation 1), and ϵ_{ij} is a random variable with mean zero and variance σ^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 η and ϵ 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,[26] was used to deter-

TABLE 2. Regression Analysis: Two- *versus* Three-compartment Model

Model	$\overline{CL}$ (l/min)	$\overline{V}_c$ (l)	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})	k_{31} (min^{-1})	LLD
Two-compartment model	0.276	10.1	0.0609	0.0224	—	—	—
Three-compartment model	0.278	7.85	0.117	0.0775	0.0221	0.00997	142*

*$P < 0.0005$.

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 χ^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 χ^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 (σ^2) was determined. A good fit should result in similar estimates of σ^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 3. Regression Analysis: Effect of Age on CL and k_{31}

Model	$\overline{CL}_y$ (l/min)	$\overline{V}_c$ (l)	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{13} (min^{-1})	k_{31_y} (min^{-1})	F_{CL}‡	$F_{k_{31}}$‡	LLD
No influence of age	0.278	7.85	0.117	0.0775	0.0221	0.00997	—	—	—
CL corrected for age	0.333	8.10	0.105	0.0536	0.00956	0.00728	0.00258	—	34*
k_{31} corrected for age	0.282	7.93	0.100	0.0658	0.0195	0.0115	—	$6.39 \cdot 10^{-5}$	10†

* $P < 0.0005$.
† $P < 0.005$.
‡ F_{CL} and $F_{k_{31}} = 0$ for age ≦ 40 yr.

TABLE 4. Regression Analysis: Effect of Body Weight on V_c

Parameter Model	$\overline{CL}$ (l/min)	$\overline{V}_c$ (l)/ $\overline{V}_{c_w}$ (l/kg)	$\bar{k}_{12}$ (min^{-1})	$\bar{k}_{21}$ (min^{-1})	$\bar{k}_{13}$ (min^{-1})	$\bar{k}_{31}$ (min^{-1})	F_{CL}†	$F_{k_{31}}$†	LLD
V_c independent of BW	0.333	8.01 (l)	0.110	0.0554	0.00965	0.00762	0.00264	$0.857 \cdot 10^{-5}$	—
V_c expressed per kgBW	0.371	0.127 (l/kg)	0.108	0.0707	0.0182	0.0131	0.00245	0.000114	24*

* $P < 0.0005$.

† F_{CL} and $F_{k_{31}} = 0$ for Age ≦ 40 yr.

TABLE 5. Regression Analysis: Effect of Sex on V_c

Parameter Model	$\overline{CL}$ (l/min)	$\overline{V}_c$ (l/kg)	$\bar{k}_{12}$ (min^{-1})	$\bar{k}_{21}$ (min^{-1})	$\bar{k}_{13}$ (min^{-1})	$\bar{k}_{31}$ (min^{-1})	F_{CL}†	$F_{k_{31}}$†	F_{sex}	LLD
No influence of sex	0.371	0.127	0.108	0.0707	0.0182	0.0131	0.00245	0.000114	—	—
V_c corrected for sex	0.356	0.111	0.102	0.0673	0.0170	0.0126	0.00267	0.000097	1.15 (M) 1.00 (F)	14*

* $P < 0.0005$.

† F_{CL} and $F_{k_{31}} = 0$ for Age ≦ 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:

$$\hat{CL}_j = \overline{CL}_y - F_{CL} \cdot (Age_j - 40) \quad (7)$$

TABLE 6. Estimates of Fixed Effects

Parameter		NONMEM Estimates (±SE)
CL (l/min)	Age ≦ 40	0.356 (±0.031)
CL (l/min)	Age > 40	0.356 − [0.00269 · (Age − 40)]
k_{12} (min^{-1})		0.104 (±0.014)
k_{21} (min^{-1})		0.0673 (±0.0165)
k_{13} (min^{-1})		0.0170 (±0.0111)
k_{31} (min^{-1})	Age ≦ 40	0.0126 (±0.00398)
k_{31} (min^{-1})	Age > 40	0.0126 − [0.000113 · (Age − 40)]
V_c (l/kg)	Male	0.111 (±0.00895)
V_c (l/kg)	Female	0.111 · 1.15

TABLE 7. Estimates of Random Effects

Parameter	NONMEM Estimates* (±SE)
Interindividual variability of CL†	48% (±9)
Interindividual variability of V_c†	33% (±6)
Residual intraindividual variability	25% (±2)

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

and

$$\hat{k}_{31_j} = \bar{k}_{31_y} - F_{k_{31}} \cdot (Age_j - 40) \quad (8)$$

where $\hat{CL}_j$ and $\hat{k}_{31_j}$ are corected estimates for patient j aged Age_j; $\overline{CL}_y$ and $\bar{k}_{31_y}$ are mean population values for young patients (≦40 yr); and F_{CL} and $F_{k_{31}}$ 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:

$$\hat{V}_{c_j} = \overline{V}_{c_w} \cdot BW_j \quad (9)$$

where $\hat{V}_{c_j}$ defines the estimate of the central compartment volume (in l) of patient j, BW_j is the body weight in kg, and $\overline{V}_{c_w}$ 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_c by body weight raised to a power different from 1 (*i.e.*, $\hat{V}_{c_j} = \overline{V}_{c_w} \cdot BW_j^F$), but no improvement of the prediction of V_c was achieved by including this additional parameter.

Sex

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

$$\hat{V}_{c_j} = \overline{V}_{c_w} \cdot BW_j \cdot F_{sex} \quad (10)$$

where F_{sex} represents the effect of sex on V_c 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_c, 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_c 33%. A significant correlation between CL and V_c 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 Stoeckel[15] 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 studies[12–15] 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 model[12,13] 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_c 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

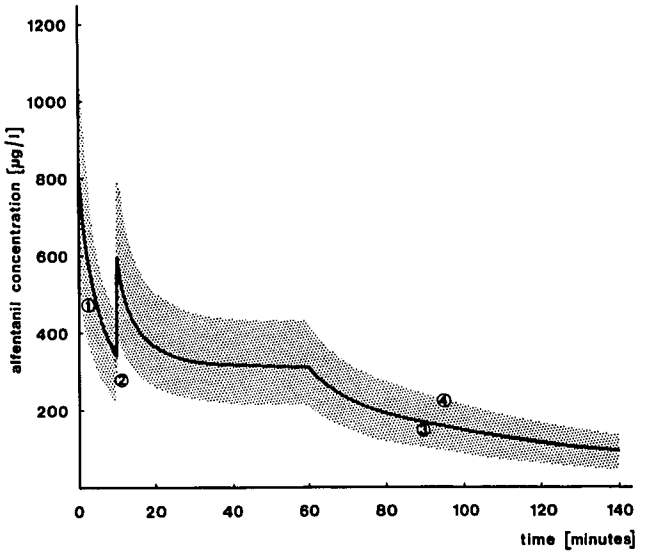

FIG. 4. Predicted plasma concentration of alfentanil (*solid line*) and 68% confidence interval (*shaded area*) calculated for a 70-yr-old female weighing 48 kg. Dosage: initial loading dose of 110 µg/kg, maintenance infusion rate of 87 µg/min up to the 60th min, bolus dose of 1.5 mg before skin incision. CP_{50} for: ① intubation; ② skin incision; ③ skin closure; and ④ spontaneous respiration after terminating N_2O.

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 intercompartmental 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, for 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 Cp_{50} 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 "Cp_{50} for laryngoscopy" after the loading dose and above the "Cp_{50} for skin incision" at the time the surgeon starts the nociceptive stimulation (fig. 4). To assume rapid recovery, the upper confidence limit should lie below the "Cp_{50} 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.[28–30] 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.[30] 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.[2]

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Appendix 1

```
100 REM ** PREDICTION OF PLASMA CONCENTRATION OF ALFENTANIL AND
110 REM ** ITS 68% LOWER AND UPPER CONFIDENCE BOUNDS
120 REM ** P.MAITRE, MD  DEPARTMENT OF ANESTHESIOLOGY
130 REM ** UNIVERSITY HOSPITAL BASEL     SWITZERLAND
140 REM ** ANSI BASIC (MICROSOFT BASIC-80 REL 5.0)
150 DEFDBL A-H,K-L,O-Z:REM DEFINE CALCULATION IN DOUBLE PRECISION (8)
160 DEFINT I-J,M-N    :REM EXCEPT FOR COUNTERS
170 REM
180 GOSUB 1000 : REM INDIVIDUALIZATION OF PHARMACOKINETIC PARAMETERS
190 GOSUB 2000 : REM DRUG INPUT (IV BOLUS AND INFUSION RATES)
200 GOSUB 3000 : REM TRANSFORMATION OF MICROCONSTANTS Kij INTO HYBRID RATE
210              REM CONSTANTS LAMBDA 1  LAMBDA 2 AND LAMBDA 3
220 GOSUB 4000 : REM PREDICTION ALGORITHM
230 END
1000 REM ************************************************************************
1010 REM ** CALCULATION OF PHARMACOKINETIC PARAMETERS ACCORDING TO
1020 REM ** AGE, GENDER AND BODY WEIGHT  (SEE TABLE 6 AND 7)
1030 INPUT "AGE " ;AGE :LPRINT "AGE     ";AGE
1040 INPUT "SEX (M or F) ";SEX$:LPRINT "SEX     ";SEX$
1050 INPUT "BODY WEIGHT IN KG ";BW:LPRINT "BW      ";BW
1060 K12 = .102                          :REM     \
1070 K21 = .0673                         :REM      \
1080 K13 = .0117                         :REM       \
1090 K31 = .0126                         :REM        \   SEE
1100 CLEARANCE = .356                    :REM        /   TABLE 6
1110 IF AGE < 40 THEN GOTO 1140          :REM       /
1120 K31 = .0126 - .000113 * (AGE - 40):REM      /
1130 CLEARANCE = .356 - .00267 * (AGE - 40):REM/
1140 VOLUME = .111 * BW :REM  VOLUME OF THE CENTRAL COMPARTMENT
1150 IF SEX$ = "F" THEN  VOLUME =  .111 * BW * 1.15
1160 OMEGASQ(1,1) = .155  :REM >> THE ARRAY OMEGASQ IS THE COVARIANCE
1170 OMEGASQ(1,2) = .0515 :REM  MATRIX OF THE ERROR TERMS ETA (INTER -
1180 OMEGASQ(2,1) = .0515 :REM  -INDIVIDUAL VARIABILITY) [EQ 5-5] <<
1190 OMEGASQ(2,2) = .0819 :REM >> SIGMASQ IS THE VARIANCE OF THE ERROR TERM
1200 SIGMASQ  = .0519     :REM  EPSILON (INTRAINDIV. VARIABILITY) [EQ 6] <<
1210 RETURN
2000 REM ************************************************************************
2010 REM ** DRUG INPUT CHARACTERISTICS
2020 INPUT "TIME LIMIT OF PREDICTION (in Min) "; TEND
2030 PRINT:PRINT "Time interval between two inputs"
2040 PRINT "must be more than ";TEND/1001" MIN":PRINT
2050 PRINT "    TIME","IV BOLUS","INFUSION RATE"
2060 LPRINT "  TIME","IV BOLUS","INFUSION RATE"
2070 PRINT "     (min)","(mg)","(ug/min)        (MAX 10X)"
2080 LPRINT "  (min)","(mg)","(ug/min)        (MAX 10X)"
2090 FOR I = 0 TO 9
2100    PRINT I;:INPUT T(I):LPRINT T(I),
2110    PRINT "  ";:INPUT B
2120    BOL(I) = B * 1000:LPRINT B,
2130    PRINT "  ";:INPUT;DINFR(I):PRINT:LPRINT DINFR(I)
2140    IF T(I) = 0 AND (BOL(I) = 0 AND DINFR(I) =0) THEN NI = I-1: GOTO 2170
2150 NEXT I                          :REM >> NI = TOTAL NUMBER OF DOSES
2160 NI = 10                         :REM (IV BOLUS, INFUSION OR BOTH) <<
2170 RETURN
3000 REM ************************************************************************
3010 REM ** TRANSFORMATION OF MICROCONSTANTS Kij INTO HYBRID RATE
3020 REM ** CONSTANT LAMBDA 1  LAMBDA 2  AND LAMBDA 3, WHICH ARE THE
3030 REM ** ROOTS OF A CUBIC EQUATION  X^3 + B2*X^2 + B1*X + B0 = 0
3040 REM ** (SEE VALUE OF B2,B1,B0 BELOW).
3050 FOR I = 1 TO 3
3060    IF I = 1 THEN CL = CLEARANCE: VC = VOLUME
3070    IF I = 2 THEN CL = CLEARANCE * 1.001:VC = VOLUME : REM >> CALCULATES
3080    IF I = 3 THEN CL = CLEARANCE: VC = VOLUME * 1.001: REM LAMBDAS WITH
3090                               REM PARAMETER VALUE SHIFTED; NEEDED FOR
3100                               REM NUMERICAL PARTIAL DERIVATIVES BELOW <<
3110    K10 = CL/VC   :REM ELIMINATION RATE CONSTANT
3120    B0 = K10 * K31 * K21
3130    B1 = K10*K31 + K21*K31 + K21*K13 + K10*K21 + K31*K12
3140    B2 = K10 + K12 + K21 + K13 + K31
3150    PHI2 = 3.14159 *2/3
3160    PHI3 = 3.14159 *4/3
3170    P = B1-(B2*B2/3)
3180    Q = (2*B2*B2*B2/27)-(B1*B2/3)+B0
3190    R = SQR(-(P*P*P)/27)
3200    COSPHI = (-Q/2)/R
3210    ACOS =-ATN(COSPHI/SQR(-COSPHI*COSPHI+1))+1.5708:REM >> APPROXIMATION
3220    PHI = ACOS :REM  OF ARCCOS(COSPHI) SINCE THE FUNCTION ARCCOS(X)
3230    R1 = 2*EXP(LOG(R)/3) :REM DOES NOT EXIST IN BASIC <<
3240    COS1 = COS(PHI/3)
3250    COS2 = COS(PHI/3 + PHI2)
3260    COS3 = COS(PHI/3 + PHI3)
3270    X(1) = -R1*COS1 + B2/3
3280    X(2) = -R1*COS2 + B2/3
3290    X(3) = -R1*COS3 + B2/3
3300    FOR II = 1 TO 3:REM THIS LOOP SORTS THE ROOTS IN A DECREASING ORDER
3310       FOR JJ = II + 1  TO 3
3320          IF X(II) > X(JJ) THEN GOTO 3340
3330          TEMP = X(II) : X(II) = X(JJ) : X(JJ) = TEMP
3340       NEXT JJ
3350    NEXT II
3360    FOR N = 1 TO 3
3370       L(N,I) = X(N)
3380    NEXT N
3390 NEXT I
3400 LPRINT  "TERMINAL ELIM. HALF LIFE (MIN) = " ;USING "###.#";.693#/L(3,1)
3410 RETURN
4000 REM ************************************************************************
4010 REM ** PREDICTIVE ALGORITHM  (SUPERPOSITION PRINCIPLE)
4020 LPRINT:LPRINT:LPRINT
4030 LPRINT "TIME       CONC.        68% CONFIDENCE INTERVAL":LPRINT
4040 J = 0:REM COUNTS HOW MANY INPUTS HAVE ALREADY BEEN ADMINISTERED AT TIME T
4050 FOR I = 0 TO 100
4060    T = I * TEND/100
4070    IF J = NI THEN GOTO 4110
4080    IF T >= T(J+1) THEN T = T(J+1): J = J+1
4090    IF J > NI THEN J = NI
4100    IF T > T(NI) THEN GOTO 4110
4110    FOR M = 1 TO 3
4120       A = 0
4130    IF M = 1 THEN CL = CLEARANCE: VC = VOLUME :REM >> LOOP FOR
4140             REM CALCULATION OF THE PREDICTED CONCENTRATION <<
4150    IF M = 2 THEN CL = CLEARANCE * 1.001:VC = VOLUME :REM >> CALCULATES
4160    IF M = 3 THEN CL = CLEARANCE: VC = VOLUME * 1.001:REM CONCENTRATION
4170                          REM WITH PARAMETER VALUE SHIFTED; NEEDED
4180                          REM FOR NUMERICAL PARTIAL DERIVATIVES BELOW <<
4190    FOR N = 0 TO J :REM >> THIS LOOP USES SUPERPOSITION PRINCIPLE TO
4200       IF T < T(N+1) THEN DINFT = T-T(N) :REM CALCULATE THE AMOUNT A IN
4210       IF N = NI THEN DINFT = T-T(N):GOTO 4230 :REM CENTRAL COMPARTMENT
4220       IF T >= T(N+1) THEN DINFT = T(N+1)-T(N) :REM AT TIME T <<
4230       DIN(1) = BOL(N) + (DINFR(N)/(-L(1,M)))*(1# - EXP(L(1,M)*(DINFT)))
4240       DIN(2) = BOL(N) + (DINFR(N)/(-L(2,M)))*(1# - EXP(L(2,M)*(DINFT)))
4250       DIN(3) = BOL(N) + (DINFR(N)/(-L(3,M)))*(1# - EXP(L(3,M)*(DINFT)))
4260       C(1) = (K21-L(1,M))*(K31-L(1,M))/((L(2,M)-L(1,M))*(L(3,M)-L(1,M)))
4270       C(2) = (K21-L(2,M))*(K31-L(2,M))/((L(1,M)-L(2,M))*(L(3,M)-L(2,M)))
4280       C(3) = (K21-L(3,M))*(K31-L(3,M))/((L(1,M)-L(3,M))*(L(2,M)-L(3,M)))
4290       F = 0
4300       FOR M1 = 1 TO 3
4310             F = F + DIN(M1) * C(M1) * EXP(-L(M1,M)*(T-T(N)))
4320       NEXT M1
4330       A = A + F
4340    NEXT N
4350    CP(M) = A/VC
4360 NEXT M
4370 CONC = CP(1): REM PREDICTED PLASMA CONCENTRATION
4380 DCCL = (CP(2)-CONC)/(CLEARANCE*.001):REM >> PARTIAL DERIVATIVES OF
4390 DCVC = (CP(3)-CONC)/(VOLUME*.001):REM THE PREDICTED CONCENTRATION WITH
4400 REM RESPECT TO CLEARANCE(DCCL)AND VOLUME OF THE CENTRAL CMPT(DCVC) <<
4410 G(1) = DCCL * CLEARANCE :REM >> PARTIAL DERIVATIVES OF THE PREDICTED
4420 G(2) = DCVC * VOLUME :REM CONCENTRATION WITH RESPECT TO ETA(CL)
4430                          REM AND ETA(VC) [SEE EQ 3 AND 5 ] <<
4440 REM
4450 REM CALCULATION OF 68% CONFIDENCE INTERVAL OF THE PREDICTED CONC.
4460 VARCP = G(1)*OMEGASQ(1,1)*G(1) + G(1)*OMEGASQ(1,2)*G(2)
4470 VARCP = VARCP + G(2)*OMEGASQ(2,1)*G(1) + G(2)*OMEGASQ(2,2)*G(2)
4480 VARCP = VARCP  + (CONC^2)*SIGMASQ : REM >> USES FIRST TERM TAYLOR
4490                          REM SERIES APPROXIMATION TO CALCULATE VARIANCE
4500                          REM OF PREDICTED CONCENTRATION [SEE EQS 3-6 FOR
4510                          REM ASSUMPTIONS ABOUT THE STATISTICAL MODEL] <<
4520 SD = SQR(VARCP) : REM GET STANDARD DEVIATION
4530 UPB68 = CONC + SD
4540 LOWB68 = CONC - SD
4550 LPRINT USING "#####.#     "; T; CONC; UPB68;LOWB68
4560 NEXT I
4570 RETURN
4580 REM ************************************************************************
```

OUTPUT SAMPLE (SEE FIG. 4)

```
AGE       70
SEX        F
BW        48
 TIME          IV BOLUS       INFUSION RATE
 (min)         (mg)           (ug/min)          (MAX 10X)
 0              5.75           87
 10             1.5            87
 60             0              0
 0              0              0
TERMINAL ELIM. HALF LIFE (MIN) = 118.6


TIME       CONC.        68% CONFIDENCE INTERVAL
    0.0       938.4       1281.5        595.4
    1.0       812.5       1106.8        518.2
    2.0       710.5        966.0        454.9
    3.0       627.8        852.5        403.2
    4.0       560.9        761.0        360.8
     .
     .
     .
     .
```