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# *Linearity of Pharmacokinetics and Model Estimation of Sufentanil*

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***Background:*** **The pharmacokinetic profiles of sufentanil available in the literature are conflicting because of methodologic differences. Length of sampling and assay sensitivity are key factors involved in accurately estimating the volumes of distribution, clearances, and elimination phase. The unit disposition function of increasing doses of sufentanil were investigated and the influence of dose administered on the linearity of pharmacokinetics was assessed.**

***Methods:*** **The pharmacokinetics of sufentanil were investigated in 23 patients, aged 14–68 yr, scheduled for surgery with postoperative ventilation. After induction of anesthesia, sufentanil was administered as a short infusion (10–20 min) in doses ranging from 250 μg to 1,500 μg. Frequent arterial blood samples were gathered during and at the end of infusion, then at specific intervals up to 48 h after infusion. Plasma concentrations of sufentanil were measured by radioimmunoassay (limit of sensitivity 0.02 ng · ml$^{-1}$). The data were analyzed with the standard two-stage, naive pooled-data and the mixed effect pharmacokinetic approaches.**

***Results:*** **The pharmacokinetics of sufentanil were adequately described by a linear three-compartmental mamillary model with the following parameters, expressed as log mean values with 95% confidence intervals: the central volume of distribution = 14.3 l (13.1–15.4 l), the rapidly equilibrating volume = 63.1 l (61.9–64.3 l), the slowly equilibrating volume = 261.6 l (260.2–262.9 l), the steady-state distribution volume = 339 l (335–343 l), metabolic clearance = 0.92 l · min$^{-1}$ (0.84–1.05 l · min$^{-1}$), rapid distribution clearance = 1.55 l · min$^{-1}$ (1.34–2.14 l · min$^{-1}$), slow distribution clearance = 0.33 l · min$^{-1}$ (0.27–0.49 l · min$^{-1}$), and elimination half-life = 769 min (690–1011 min). No relation to age, weight, or lean body mass was found for any of the parameters.**

***Conclusions:*** **Sufentanil pharmacokinetics were linear within the dose range studied. Drug detection up to 24 h after dosing was necessary to define the terminal elimination phase. The metabolic clearance approached liver blood flow and a large volume of distribution was identified, consistent with the long terminal elimination half-life. Simulations predicted that plasma sufentanil steady-state concentrations would rapidly decline after termination of an infusion despite the long half-lives. (Key words: Analgesics, opioid: sufentanil. Anesthetics, intravenous: sufentanil. Pharmacokinetics: linearity; sufentanil.)**

THE rate of onset and relative duration of effect after opioid administration depend on the distribution of the opioid in the central compartment and the biophase. The disappearance of drug effect relates to the extent of drug distribution in the body compartments, the equilibration rate constant for the biophase and the concentrations at the biophase relative to the therapeutic window. The terminal elimination half-life does not provide much insight about the decline of biophase concentration or of drug effect. The relationship between infusion duration and time required for decline of the biophase concentration after termination of opioid infusions was investigated by Shafer and Varvel[1] using computer simulations. The validity of their concepts in clinical pharmacokinetics is subject to the availability of appropriate pharmacokinetic data.

Precise kinetic information is also required for designing drug administration regimens to provide adequate plasma concentrations for the optimal biophase

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effect and thus improve the therapeutic efficacy of opioids. Predicting drug concentrations is hampered by the interindividual pharmacokinetic variability and the precision of the pharmacokinetic parameters used. The accuracy of estimation of the elimination phase, clearance, and volumes of distribution of drugs depends on the study design. Precision and sensitivity of the assay methods as well as timing and duration of sampling are important determinants. With very potent drugs, plasma concentrations may rapidly fall below the sensitivity of the drug assay method.

For opioid infusions of shorter than 8 h, sufentanil was suggested to be the most appropriate choice because it showed the fastest 50% decrement in biophase concentrations after termination of the infusion, relative to fentanyl and alfentanil.[1] The pharmacokinetics of fentanyl and alfentanil have been well established. However, there are conflicting data regarding the pharmacokinetic profile of sufentanil. Bovill *et al.*[2] administered 5 $\mu g \cdot kg^{-1}$ and were able to detect the drug for 8 h or less using venous sampling. Their pharmacokinetic profile of sufentanil will be contrasted to that of Hudson *et al.*[3] who gave 12.5 $\mu g \cdot kg^{-1}$ and detected arterial sufentanil concentrations for 12–24 h. Whereas the metabolic clearances reported by both authors were similar, the steady-state distribution volume and terminal elimination half-life varied fivefold. Dose-related changes in the disposition profile of sufentanil have not been demonstrated. An essential issue in this pharmacokinetic controversy involves the ability to detect the drug for an adequate period of time to accurately estimate the distribution and elimination kinetics.

The purposes of the current investigation were (1) to investigate whether the pharmacokinetics of sufentanil were linear with respect to dose; (2) to precisely define the distribution and elimination kinetics of sufentanil; and (3) to develop a pharmacokinetic method that accurately predicted sufentanil concentrations resulting from different dosage schemes. A wide range of sufentanil doses were studied with prolonged arterial sampling and drug detection for up to 48 h after dosing.

## Material and Methods

### *Clinical Study Design*

The study was approved by the Committee on Human Research of the Free University of Brussels. Twenty-five patients (ASA physical status 1 or 2) scheduled for head and neck surgery gave informed consent to participate in the pharmacokinetic investigation. Depending on the expected duration of surgery they received the following sufentanil dosage regimens: 25 $\mu g \cdot min^{-1}$ over 10 min (250-$\mu$g dose), 50 $\mu g \cdot min^{-1}$ over 10 min (500-$\mu$g dose), 75 $\mu g \cdot min^{-1}$ over 10 min (750-$\mu$g dose), 66.7 $\mu g \cdot min^{-1}$ over 15 min (1,000-$\mu$g dose), or 75 $\mu g \cdot min^{-1}$ over 20 min (1,500-$\mu$g dose), respectively.

All patients were premedicated with 0.2–0.4 mg intramuscular glycopyrrolate or 0.25–0.5 mg atropine, and 5–10 mg midazolam or 1–2 mg lorazepam Monitoring included electrocardiography, pulse oximetry, and blood pressure measurement. Anesthesia was induced with 0.2 $mg \cdot kg^{-1}$ intravenous etomidate. Tracheal intubation and muscle relaxation was achieved with 0.5 $mg \cdot kg^{-1}$ atracurium and mechanical ventilation was performed with 35% oxygen in nitrous oxide. End-tidal carbon dioxide was monitored to maintain normocapnia. Once patients were unconscious, a 20-G catheter was placed in the radial artery of the nondominant arm for blood sampling and continuous blood pressure monitoring. Sufentanil (50 $\mu g \cdot ml^{-1}$) was then infused according to the dose allocation of the patient using a calibrated syringe infusion pump connected to an 18-G intravenous catheter in a forearm vein and continuously flushed with Ringer lactate solution. Whenever blood pressure or heart rate increased by more than 30% such that depth of anesthesia was judged inadequate, hemodynamic control was ensured with 0.3–0.8 vol % isoflurane. Arterial blood samples were taken before and every 2 min during the sufentanil infusion, at end of infusion, at 1, 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 90, 120 min, then at hourly intervals until 8 h, every 2 h until 36 h, and at 4-h intervals until 48 h postinfusion. Blood samples were collected in heparinized tubes, centrifuged, and the plasma obtained frozen (−27°C) for storage until time of analysis. Plasma sufentanil concentrations were determined by radioimmunoassay[4] (Janssen Research Foundation, Beerse, Belgium). The limit of detection was 0.02 $ng \cdot ml^{-1}$ and the interassay coefficient of variation 8.5–10.5% for a concentration range of 0.05–10 $ng \cdot ml^{-1}$.

### *Linearity Analysis*

The pharmacokinetics of sufentanil were estimated in each person using a three-compartment mamillary pharmacokinetic model, in which drug is directly injected into the central compartment, distributes into two peripheral compartments distinguished by their rates of equilibration with the plasma, and is eliminated from the central compartment. In this approach, sub-

sequently called the "two-stage" approach, the volumes and clearances of a three-compartment pharmacokinetic model were fit to the plasma concentration *versus* time data for each subject using Microsoft Excel (v. 5.0, Microsoft Corp., Redmond, Washington). The "Solver" tool in Excel was used to minimize the extended least-squares objective function, O:

$$O = \sum_{i=1}^{n} \frac{(Y_i - \hat{Y}_i)^2}{V_i} + \mathrm{Ln}(V_i),$$

where n was the number of observations for each subject, $Y_i$ was the ith observation, $\hat{Y}_i$ was the ith predicted concentration, and $V_i$ was the predicted variance of the ith observation. $V_i$ was calculated using the constant coefficient of variation model: $Vi = (\sigma\hat{Y}_i)^2$ where $\sigma$ was the "variance scale parameter" estimated so that

$$\sum_{i=1}^{n} \frac{(Y_i - \hat{Y}_i)^2}{(\sigma\hat{Y}_i)^2} = n$$

This objective function can be transformed to −2 log likelihood (−2LL) by the addition of a constant:

$-2LL = O + n\ \mathrm{Ln}(2\pi)$

Derived pharmacokinetic parameters were calculated from the estimated volumes and clearances using standard equations[5] and included the fractional coefficients (A, B, C), the central volume of distribution, the rapidly equilibrating volume, the slowly equilibrating volume, the volume of distribution at steady-state, the metabolic clearance, the half-lives of distribution and elimination, the slow distribution clearance, and the fast distribution clearance. For each dosing group, the log mean value was calculated as well as the 95% confidence interval for the log mean estimate. The pharmacokinetic parameters between dosing groups were then compared to identify significant pharmacokinetic differences as a function of dose.

As given in the results section, the pharmacokinetic parameters in patients administered a dose of 250 μg differed significantly from the parameters of patients receiving larger doses. To verify whether these differences were real or an artifact of the analysis, we simulated the concentrations predicted by the pharmacokinetic model for each group after a bolus injection of 1 unit. The simulation was divided into two portions: those concentrations within the time actually sampled for the group (*i.e.*, based on real data), and those concentrations extrapolated beyond the times of measured blood samples. This analysis determined whether the pharmacokinetic differences in the subjects receiving 250 μg were based on the observed concentrations, or on the extrapolation of the model beyond the period of observation. We also derived individual pharmacokinetic models using just the first 8 h of data, the period for which measurable plasma sufentanil concentrations were available in all subjects. We then estimated pharmacokinetic models for each dosing group from the log mean volumes and clearances in the individual patients. These models were compared to identify whether the observed differences in pharmacokinetics in the subjects receiving 250 μg were real or an artifact of the analysis.

*Model Estimation*

The pharmacokinetics of sufentanil were further estimated using two other alternative data analysis approaches: a pooled-data approach and a mixed-effect approach. Each approach was based on a three-compartment mamillary model as was the case for the two-stage approach. These three different approaches were used because we wished to examine whether and how the pharmacokinetic estimation technique might affect the pharmacokinetic model of sufentanil estimated from different dosage schemes and different duration of sufentanil detection. Our approach was similar to that described by Kataria *et al.*[6]

**Pooled-data Approach.** For this approach, the volumes and clearances of a three compartment pharmacokinetic model were fitted to the pooled observed concentrations over time using NONMEM.†† Although NONMEM was programmed for mixed-effect modeling, it can be used for simple pooled-data modeling by fixing the estimates of the interindividual variability to 0. The objective function for the pooled-data approach becomes exactly the same as for the two-stage analysis, described earlier, except that *n* becomes the total number of observations in the study. Because all of the data were considered in a single fit, no individual subject pharmacokinetic parameters were estimated. Thus, there was no subsequent calculation of the "mean" pharmacokinetic parameter from individual estimates.[7]

**Mixed-effect Modeling Approach.** In this approach, the pharmacokinetic parameters, the interindividual variance of the pharmacokinetic parameters, and the intraindividual variance were estimated simultaneously using NONMEM. Unlike the pooled-data

†† Beal SL, Sheimer LB: NONMEM Users Guides. San Francisco, University of California, NONMEM Project Group, 1992.

approach, this approach accounted for the different persons from whom the observations arose. NONMEM also minimized −2LL, modified to account for the nesting of random effects. The NONMEM analysis used NMVCL, a Fortran subroutine for NONMEM developed by the authors to fit the volumes and clearances of three-compartment models to the data. The mixed-effect analysis assumed that variance of the residual error was proportional to the square of the predicted concentration (constant coefficient of variation variance model), consistent with the variance model used for the two-stage and pooled-data approaches.

After determining the volumes and clearances for each subject, as described earlier, the log mean volumes and clearances were calculated from those subjects receiving 500 μg, 750 μg, 1,000 μg, and 1,500 μg sufentanil The volumes and clearances from subjects receiving 250 μg were not included because their short duration of measured plasma concentrations precluded accurate pharmacokinetic parameter estimation. From the log mean volume and clearance estimates the other pharmacokinetic parameters reported earlier were derived.

The influence of age on volumes and clearances was tested using linear regression analysis of each pharmacokinetic parameter against age. Weight and lean body mass were investigated as covariates by dividing the individual estimates of volumes and clearances by the subject's weight or lean body mass, deriving the log mean volumes (in l/kg) and clearance (in $l \cdot kg^{-1} \cdot min^{-1}$) and examining the performance of the resulting model as described later. Lean body mass was calculated as:[8]

$$\text{In men: LBM} = 1.1\ \text{weight} - 128\left(\frac{\text{weight}}{\text{height}}\right)^2;$$

$$\text{In women: LBM} = 1.07\ \text{weight} - 148\left(\frac{\text{weight}}{\text{height}}\right)^2.$$

*Graphic Assessment of Goodness of Fit*

To provide a visual representation of the overall accuracy of the fits, we plotted the weighted residuals over time, superimposing the results of all 23 subjects. Because the weighted residuals in the graphs were log normally distributed, we first added 1 to the weighted residuals (to center the residuals about 1, rather than 0), and then plotted the results on a log scale. This is mathematically identical to plotting the measured/predicted concentrations on a log scale.

We also plotted the unit disposition function for each subject, as determined in the two-stage analysis, against time from the time of the first observation to the time of the last observation. We then plotted the average unit disposition function developed from the two-stage, pooled and mixed-effect approaches. This allowed graphic representation of both how well the individual unit disposition functions were described and how similar were the disposition functions estimated by the three approaches.

## Results

Of the initial 25 subjects, the data from two patients (1 receiving the 500-μg dose and 1 receiving the 750 μg dose) were discarded from the final analysis because unexpected surgical complications interfered with the normal sampling procedure. The dosage groups did not differ with respect to age and body weight ranges (table 1). Figure 1 shows all the individual patient plasma concentration *versus* time data. The data designated by the "x" symbol were considered either improbably high outliers (3 points) or were values at the limit of detection of the assay that followed samples below the limits (10 points) and were excluded from the pharmacokinetic analysis. The linearity and pharmacokinetic modeling was based on 788 of the 801 measured concentrations.

Table 2 summarizes the log mean pharmacokinetic parameters and the 95% confidence interval of the mean estimates for each dosing group. Clearances and half-lives appeared related to the dose administered, whereas the volume of distribution at steady-state was not. However, the unit disposition functions demonstrated a dose-related deviation only in the extrapolated part of the curve (fig. 2). The pharmacokinetic parameter estimation for the subjects receiving 250 μg sufentanil did not include the terminal elimination phase evident in subjects receiving larger doses. As a result, all of the half-lives appear faster in the 250-μg group. Therefore, we did not include the 250-μg group in the final model estimate from the two-stage approach.

If we confine our comparison of disposition curves to the time segments represented by the original data (fig. 2, solid lines) the pharmacokinetics in patients receiving 250 μg are the same as the pharmacokinetics in subjects receiving larger doses. Figure 3 represents the unit disposition functions generated by the two-stage approach confined to data from the first 8 h after dosing, the period during which sufentanil plasma

**Table 1. Demographics**

| | Sufentanil Dose | | | | |
|---|---|---|---|---|---|
| | 250 μg | 500 μg | 750 μg | 1,000 μg | 1,500 μg |
| Gender | | | | | |
| Male | 2 | 2 | 4 | 2 | 4 |
| Female | 3 | 2 | — | 3 | 1 |
| Age (yr) | | | | | |
| Mean | 51 | 32 | 60 | 43 | 52 |
| Range | 40–60 | 14–59 | 52–68 | 17–65 | 45–60 |
| Weight (kg) | | | | | |
| Mean | 75 | 71 | 69 | 60 | 64 |
| Range | 58–80 | 55–85 | 52–90 | 48–68 | 47–94 |
| Height (cm) | | | | | |
| Mean | 163 | 177 | 169 | 168 | 164 |
| Range | 159–169 | 171–182 | 163–173 | 165–170 | 154–172 |
| Lean body mass (kg) | | | | | |
| Mean | 50 | 55 | 54 | 47 | 49 |
| Range | 43–56 | 44–65 | 45–63 | 39–52 | 38–65 |
| Duration of surgery (h) | | | | | |
| Mean | 2.2 | 5.4 | 6.3 | 8 | 12.4 |
| Range | 0.5–3 | 4.5–7 | 5–8.5 | 6.5–10.5 | 9.5–14 |

concentrations were available in all patients from all dosage groups. The extrapolated parts of the curves, represented as dotted lines, deviated from each other in a random fashion, unrelated to the dose of sufentanil administered, and the derived pharmacokinetic parameters showed no dose relationship.

The three different pharmacokinetic approaches estimated comparable volumes and clearances for sufentanil (table 3). The mixed-effect approach estimated the largest volume of distribution at steady-state resulting in the longest terminal half-life. The coefficient of variation for the two-stage and mixed-effect approaches is actually the standard deviation of the log transformed estimates of the volumes and clearances expressed in percent, reflecting the log normal distribution of the parameters, and thus is only approximately the coefficient of variation in the conventional sense. Figure 4 shows the residual error as a function of time for all persons. Overall, the pattern of residual errors was nearly identical. The residuals for the two-stage approach showed a positive bias for the period from 1,500 min to the end of the study, whereas the mixed-effect approach showed a negative bias from 600 min to the end of the study. Figure 5 shows the individual unit disposition curves for each subject and the unit disposition curves estimated using the two-stage, pooled, and mixed-effect approaches and confirmed the negative bias obtained with the mixed-effect approach when compared with the other techniques of data analysis.

An attempt to model the volumes and clearances of sufentanil as proportional to weight and lean body mass did not improve the goodness of fit. However, the model did not deteriorate when weight or lean body mass were included as simple scalars of volumes and clearances. Thus, for the population studied, the data did not support adjusting sufentanil pharmacokinetics on the basis of weight or lean body mass. However, our results also do not suggest that such an adjustment would be detrimental to the pharmacokinetic parameter estimates. The two-stage regression analysis did not show any effect of age on the volumes, clearances, or half-lives of sufentanil.

## Discussion

The major aims of this study were: (1) to assess the linearity of sufentanil pharmacokinetics over a clinically meaningful dosing range; and (2) to develop a pharmacokinetic model that accurately predicted sufentanil concentrations resulting from any arbitrary drug input. The latter goal obviously is predicated on demonstration of linearity. Unique features of this sufentanil pharmacokinetic study include the prolonged duration of sampling, the dose range of sufentanil ad-

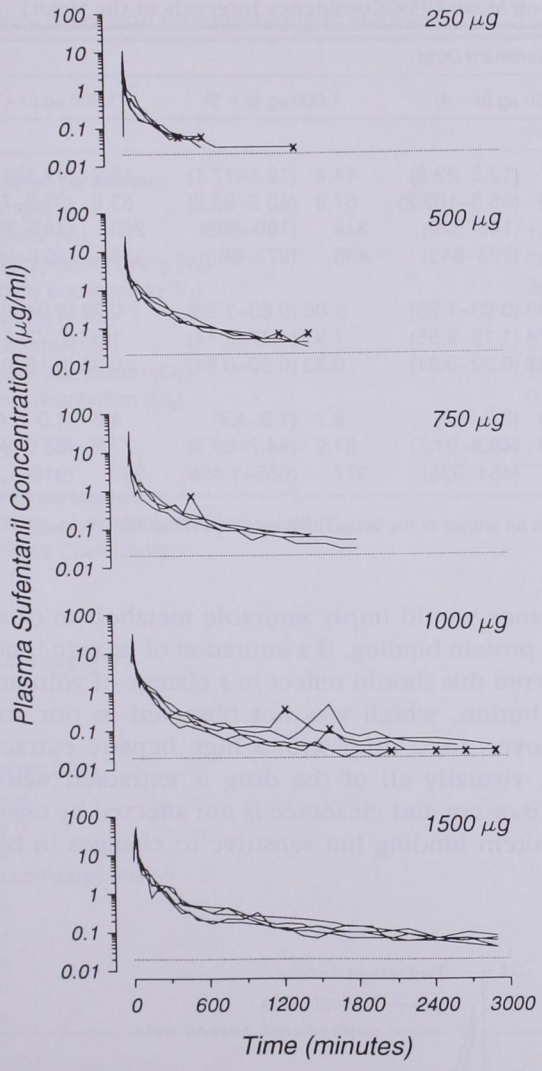


**Fig. 1. Individual patient plasma sufentanil concentration *versus* time curves for each dosage group. The horizontal dashed line indicates the level of sensitivity of the radioimmunoassay (0.02 ng · ml$^{-1}$). Data deleted from the analysis are marked by an "x."**

ministered, the sensitive assay and the use of three different model estimation approaches.

*Linearity Analysis*

The standard method of assessing linearity with respect to dose is to administer increasing doses and observe that maximum concentration and the area under the concentration *versus* time curve, both scale in proportion to the administered dose. This approach is not satisfactory for intravenous drugs with polyexponential disposition functions because there might be offsetting changes in the volumes or clearances with increasing dose so that maximum concentration/dose or area under the concentration *versus* time curve/dose do not change despite nonlinearity. Additionally, the area under the concentration *versus* time curve depends on the extrapolation of the concentration *versus* time curve to infinity and this extrapolation might differ for different doses simply because the concentrations resulting from smaller doses would fall below the levels of detection earlier, as observed in this study. A second method of assessing linearity is to demonstrate that the concentrations are identical when divided by the dose. This approach, although robust, requires the same time course of drug administration. In the current study, simple normalization of concentrations to dose was not possible because the infusions of drug were of different durations.

A third method of assessing linearity is to compute the pharmacokinetic parameters in groups receiving different doses, and then look for changes in the parameters as a function of dose. This common approach is potentially misleading, as we demonstrate herein. The metabolic clearance of sufentanil in subjects receiving 250 μg was greater, and the half-life of distribution was shorter, than for the other groups. Although these findings were statistically significant, we show that they were also artifacts of the data analysis. The plasma sufentanil concentrations in subjects receiving 250 μg consistently fell below the limits of detection before the terminal phase. Thus, all of the half-lives were shortened relative to the other groups, and the clearance was increased accordingly.

To demonstrate that the pharmacokinetics were the same in the 250-μg group, we compared the segment of the disposition curve for the 250-μg group that was derived directly from observed data with the disposition curves for the other groups. This analysis, shown in figure 2, demonstrated that when confined to the portion of the curve based directly upon observed concentrations, the predicted sufentanil concentration after a bolus input of 1 unit is independent of dose, within the range studied. Figure 3 supplements this analysis by demonstrating that similar disposition functions are observed for all groups when estimated from only the first 8 h of data. This also suggests a lack of dose-dependent pharmacokinetics.

In comparing disposition functions between groups, we are actually comparing the dose-normalized concentrations, but in a manner that also normalizes for time of drug administration. Thus, comparing dispo-

**Table 2. Derived Pharmacokinetic Values for Each Dose of Sufentanil: Log Mean (95% Confidence Intervals of the Mean)**

| | Sufentanil Dose | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 250 μg* (n = 5) | | 500 μg (n = 4) | | 750 μg (n = 4) | | 1,000 μg (n = 5) | | 1,500 μg (n = 5) | |
| Volume (l) | | | | | | | | | | |
| Central ($V_1$) | 15.3 | (11.8–19.9) | 11.2 | (8.3–15.2) | 16.7 | (12.2–22.8) | 14.4 | (12.1–17.1) | 15.2 | (12.1–19.0) |
| Rapidly equilibrating ($V_2$) | 36.6 | (15.4–87.1) | 59.0 | (37.3–93.4) | 75.2 | (55.3–102.2) | 67.9 | (48.5–95.2) | 53.9 | (37.9–76.5) |
| Slowly equilibrating ($V_3$) | 138 | (70–274) | 174 | (115–262) | 278 | (146–529) | 344 | (199–595) | 263 | (189–367) |
| Steady state ($V_{SS}$) | 200 | (110–363) | 246 | (166–364) | 380 | (224–643) | 436 | (273–695) | 336 | (251–449) |
| Clearance ($l \cdot min^{-1}$) | | | | | | | | | | |
| Systemic ($Cl_1$) | 1.37 | (1.08–1.73) | 0.88 | (0.73–1.07) | 1.03 | (0.83–1.28) | 1.06 | (0.89–1.26) | 0.76 | (0.64–0.89) |
| Rapid distribution ($Cl_2$) | 2.40 | (1.29–4.46) | 1.67 | (0.97–2.90) | 1.74 | (1.19–2.55) | 1.91 | (1.17–3.14) | 1.07 | (0.73–1.58) |
| Slow distribution ($Cl_3$) | 0.85 | (0.39–1.84) | 0.33 | (0.20–0.54) | 0.45 | (0.22–0.91) | 0.33 | (0.20–0.54) | 0.25 | (0.18–0.35) |
| Half-lives (min) | | | | | | | | | | |
| $t_{1/2}\ \alpha$ | 1.9 | (1.5–2.5) | 2.5 | (1.5–3.9) | 3.3 | (2.7–3.9) | 2.7 | (1.8–4.2) | 4.6 | (4.0–5.4) |
| $t_{1/2}\ \beta$ | 23.5 | (11.8–47.0) | 60.9 | (43.2–85.7) | 67.0 | (48.9–91.7) | 61.9 | (44.7–85.7) | 77.2 | (63.0–94.6) |
| $T_{1/2}\ \gamma$ | 202 | (129–316) | 526 | (342–809) | 650 | (451–935) | 977 | (655–1,458) | 999 | (916–1,089) |

* Note the appearance of dose-dependent pharmacokinetics. As explained in the text, this is an artifact of the limited data detection in the 250 μg group.

sition functions permits direct comparison of pharmacokinetics when the time course of drug administration differs between groups, as it did in this study. When the segments derived directly from observed data are distinguished from the segments extrapolated beyond the observed data, we can see the artifact caused by the extrapolation, as observed in the 250-μg group in this study. These findings agree with our *a priori* expectation that sufentanil pharmacokinetics would be linear with respect to dose. A dose related decrease in clearance would imply saturable metabolism or saturable protein binding. If a saturation of protein binding occurred this should reflect in a change of volumes of distribution, which was not observed in our study. Moreover, for a drug with a high hepatic extraction ratio, virtually all of the drug is extracted whether bound or not and clearance is not affected by changes in protein binding but sensitive to changes in blood flow.

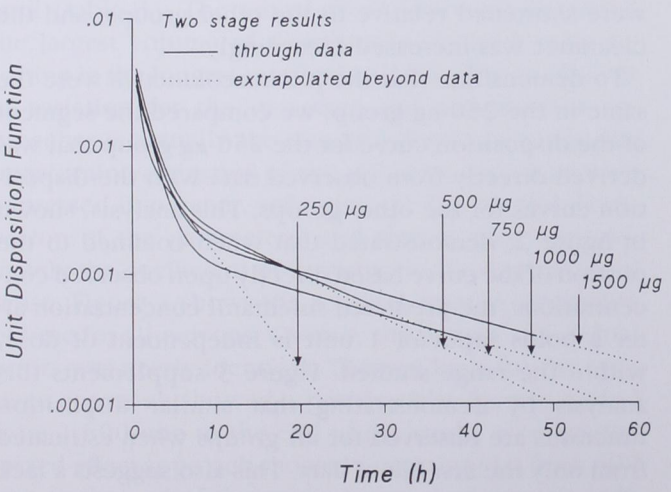


**Fig. 2. The unit disposition curves (*i.e.*, the expected concentrations after a bolus dose of one unit) generated from the log mean parameters of each group by the two-stage pharmacokinetic approach on all available data. The solid line represents the time period during which observations were made, the dotted line represents the extrapolated part of the curve.**

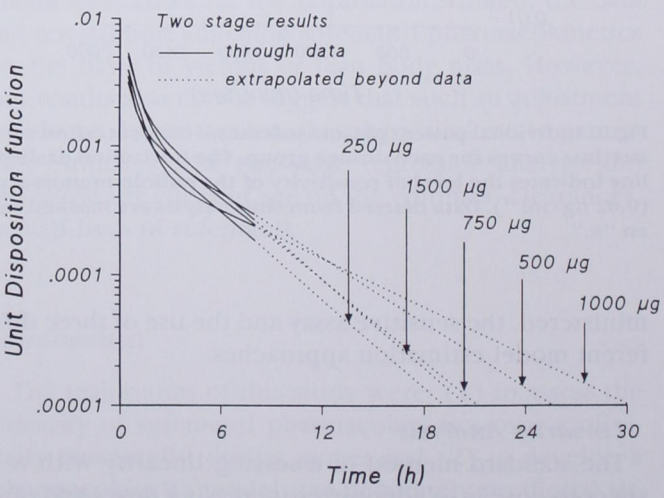


**Fig. 3. The unit disposition curves (*i.e.*, the expected concentrations after a bolus dose of one unit) generated from the log mean parameters of each group by the two-stage pharmacokinetic approach confined to the concentration data from the first 8 h after dosing. The solid line represents the time period during which observations were made, the dotted line represents the extrapolated part of the curve.**

**Table 3. Sufentanil Pharmacokinetic Models**

| | Two-stage (n = 18) | | Pooled (n = 23) (nominal) | Mixed-effect (n = 23) | |
|---|---|---|---|---|---|
| | Nominal | CV (%) | | Nominal | CV (%) |
| Estimated parameters | | | | | |
| Volume (l) | | | | | |
| Central ($V_1$) | 14.3 | 28 | 16.6 | 14.6 | 22 |
| Rapidly equilibrating ($V_2$) | 63.1 | 38 | 72 | 66 | 31 |
| Slowly equilibrating ($V_3$) | 261.6 | 54 | 398 | 608 | 76 |
| Clearance ($l \cdot min^{-1}$) | | | | | |
| Systemic ($Cl_1$) | 0.92 | 23 | 0.90 | 0.88 | 23 |
| Rapid distribution ($Cl_2$) | 1.55 | 51 | 1.4 | 1.7 | 48 |
| Slow distribution ($Cl_3$) | 0.33 | 54 | 0.36 | 0.68 | 78 |
| | Nominal | | Nominal | Nominal | |
| Derived parameters | | | | | |
| Volume of distribution steady state ($V_{ss}$) (l) | 339 | | 487 | 689 | |
| Fractional Coefficients | | | | | |
| A | 0.93 | | 0.93 | 0.94 | |
| B | 0.068 | | 0.064 | 0.058 | |
| C | 0.0041 | | 0.0037 | 0.0048 | |
| Exponents ($min^{-1}$) | | | | | |
| $\alpha$ | 0.2152 | | 0.17 | 0.24 | |
| $\beta$ | 0.0104 | | 0.009 | 0.012 | |
| $\gamma$ | 0.0009 | | 0.0006 | 0.0006 | |
| Half-lives (min) | | | | | |
| $t_{1/2}\ \alpha$ | 3.3 | | 4.0 | 2.9 | |
| $t_{1/2}\ \beta$ | 67 | | 79 | 59 | |
| $t_{1/2}\ \gamma$ | 769 | | 1092 | 1129 | |
| Rate constants ($min^{-1}$) | | | | | |
| $K_{10}$ | 0.0645 | | 0.05 | 0.06 | |
| $k_{12}$ | 0.1086 | | 0.09 | 0.11 | |
| $k_{13}$ | 0.0229 | | 0.02 | 0.05 | |
| $k_{21}$ | 0.0245 | | 0.020 | 0.025 | |
| $k_{31}$ | 0.0013 | | 0.0009 | 0.0011 | |

Nonlinearity of the disposition kinetics due to enzyme activity limitations is rare when a high hepatic extraction ratio exists because a high extraction ratio implies that the intrinsic organ clearance is greatly in excess of organ blood flow.[5] Hepatic blood flow alterations induced by the infusion rates of sufentanil used for the high doses are unlikely. During high-dose (20 $\mu g \cdot kg^{-1}$) sufentanil anesthesia[9] no effects on cardiac index were reported while sufentanil infusion rates fourfold higher than those used in our study decreased cardiac index and systemic vascular resistance by 13%.[10]

We have demonstrated that conventional analysis of linearity may incorrectly suggest dose-dependent pharmacokinetics when the duration of measured concentrations is a function of the administered dose. The comparison of the unit disposition curves over the period of directly observed data permits an analysis of linearity that is properly dose-normalized in both the concentration and time domains. Such an analysis demonstrates that sufentanil pharmacokinetics are linear with respect to dose.

*Optimal Model Identification*

The two-stage model was developed from the log mean volumes and clearances in subjects receiving 500-$\mu$g, 750-$\mu$g, 1,000-$\mu$g, and 1,500-$\mu$g doses. Because the volumes and clearances in subjects receiving only 250 $\mu$g were incorrect because of the limited duration of the drug detection, they were not included in the two-stage analysis.

In attempting to identify an optimal model, we repeated some of the analyses performed by Kataria *et al*

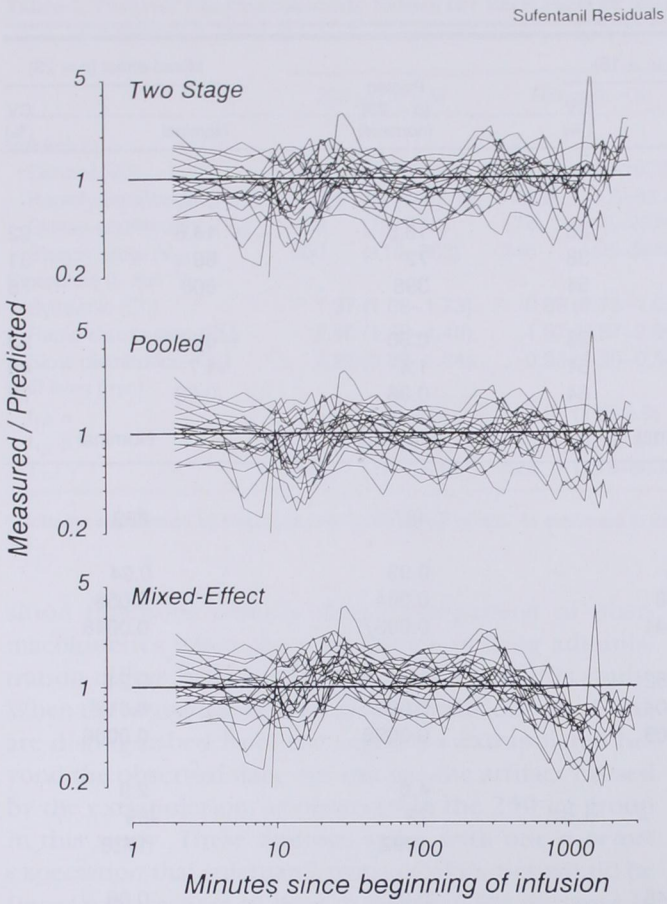


**Fig. 4. The residual errors, expressed as measured/predicted concentration, for all 23 subjects for the three pharmacokinetic approaches.**

for propofol.[6] In their study, the two-stage, pooled, and mixed-effect approaches provided virtually indistinguishable models. In the current study, the models were similar, but not indistinguishable. The model estimated using a mixed-effect approach was clearly inferior to the models estimated using the two-stage and pooled-data approaches. The "best" model from this analysis was that developed using the two-stage approach. This model described the observations well and it better reflected the central tendency of the terminal portion of the disposition function. We do not mean to imply by our results that the two stage approach is, in general, superior to other approaches. There are examples in which the "naive" pooled-data approach has proved robust,[6] and other examples in which a mixed-effect model is the preferred approach.[11]

The lack of influence of weight on sufentanil pharmacokinetics suggests that, within the weight range studied, sufentanil dosing need not be adjusted for weight. This conclusion may not apply to persons at the extremes of weight, who were not included in the study population. In the two-stage analysis, no correlation was found between any of the pharmacokinetic parameters and age. This lack of an influence of age on sufentanil pharmacokinetics is consistent with the report by Helmers *et al.* that age-related differences in action of sufentanil could not be explained by its changes in pharmacokinetics with age.[12] This was at variance with the previous data from Matteo *et al.*, who observed a significant increase of initial volume of distribution of sufentanil in elderly patients.[13]

In comparing our model with previous investigations, it is important to recall that the pharmacokinetics of sufentanil may appear to differ strictly because of different durations of sampling, as we demonstrated in the 250-μg group. For example, Bovill *et al.* sampled venous blood for 8 h after a bolus intravenous injection and reported a short elimination half-life of 164 min.[2] The results of Hudson *et al.*, who sampled arterial blood for 24 h, are in good agreement with our model.[3] Other authors studied the sufentanil disposition kinetics in specific populations. Chauvin *et al.* studied healthy and patients with cirrhosis patients and reported an elimination half-life of respectively 210 and 246 min from a 10-h sampling duration,[14] similar to the elimination half-life of our 250-μg dose. Short elimination half-lives were reported in neurosurgical adult patients sampled for 240 min[15] and in renal failure patients sampled for only 180 min.[16] In all of these cases, the short duration of sampling likely resulted in significant error in the estimation of the terminal elimination phase, with underestimation of the volume of distribution and/or overestimation of clearance. Our results suggest that sufentanil must be measured for at least 24 h to accurately define the terminal elimination phase of the sufentanil disposition function.

Recent reports demonstrate that the rate of decline of plasma concentrations after usual clinical administration cannot be predicted simply from the half-lives of the drug.[17,18] The intercepts of the slopes of the decay curve, expressed as percent of the initial plasma concentration, offer insight in the relative importance of each half-life to the drug concentration decline. The fractional intercept of the terminal elimination phase of sufentanil was 0.41%. Thus, this phase contributes almost nothing to the decline in plasma concentration

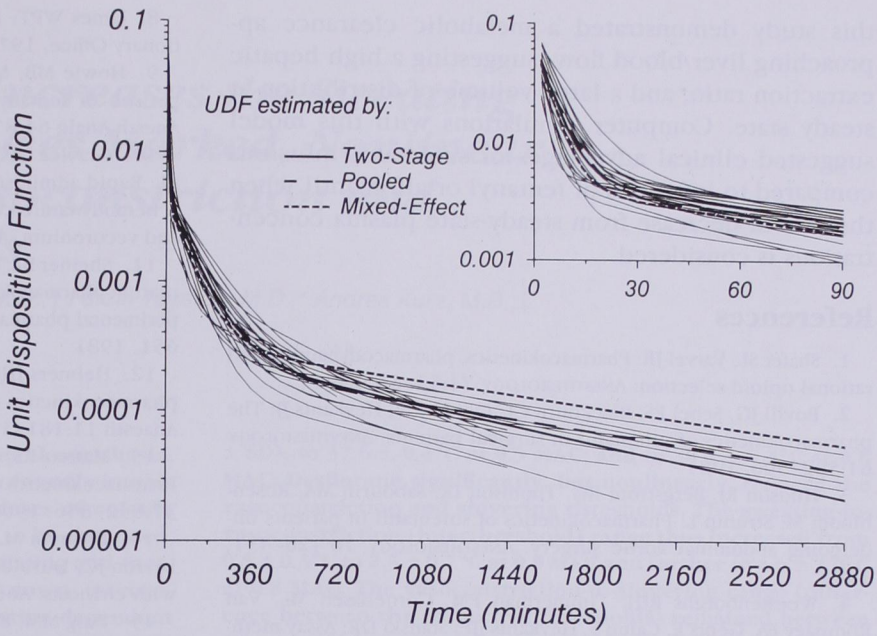


**Fig. 5. The individual disposition functions (*i.e.*, the expected concentrations after a bolus dose of one unit) for all 23 subjects and the disposition functions generated by the three pharmacokinetic models. The inset expands the first 90 min.**

after a bolus injection. None of the parameters of the three compartment pharmacokinetic model quantitates or predicts to what extent the concentration decline of a drug might be prolonged after repetitive dosing or drug infusion. A "context sensitive half-time" was defined by Hughes *et al.* as the time required for the drug plasma concentration to decline by 50% after a given duration of drug infusion.[18] As noted by Shafer and Stanski,[17] the time for a 50% decrement in plasma concentration may not define the time required for clinical recovery. Figure 6 shows the time required for the plasma sufentanil concentration to decrease by 30%, 50%, and 70% after termination of an infusion, based on the two-stage model from this analysis, and the models reported by Bovill *et al.*[2] and Hudson *et al.*[3] After an infusion of up to 2 h duration, the 50% decrement time increases with infusion duration. After 2 h, the slopes flatten. Although we report longer half-lives, our pharmacokinetics predict the most rapid decrease in plasma concentration after termination of an infusion, particularly for infusions of greater than 6 h duration. However, all three sufentanil parameter sets produce similar estimations of the time required for 30%, 50%, and 70% decrement. This likely results from (1) the significant influence of the early, rapid pharmacokinetic components on the decrement time after infusion termination and (2) all three studies probably correctly characterized these rapid components, despite differences in study design and sampling duration.

In conclusion, this study demonstrated that the disposition function of sufentanil is linear with respect to dose. Precise estimation of the clearances and volumes of distribution requires sufentanil doses greater than 500 μg, given the sensitivity of the drug assays available, and blood sampling of at least 24 h. The optimal sufentanil pharmacokinetic model developed in

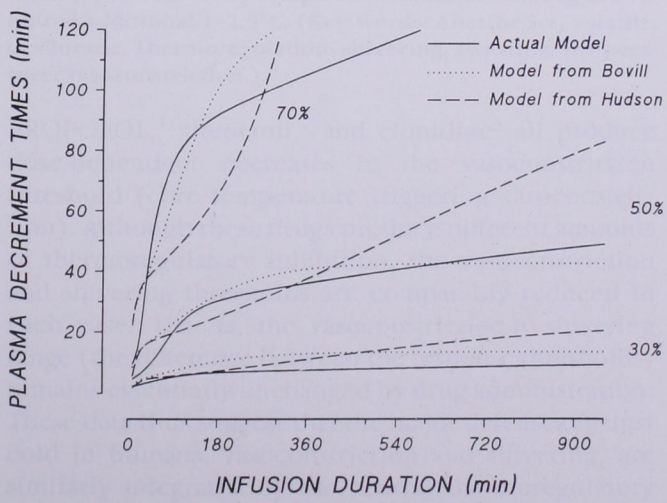


**Fig. 6. Time for the plasma sufentanil concentration to decrease by 30%, 50%, and 70% after the termination of a sufentanil infusion up to 16 h. The solid, dotted and dashed lines were generated using, respectively, the actual two-stage pharmacokinetic model, the model from Bovill *et al.*[2] and the model from Hudson *et al.*[3]**

this study demonstrated a metabolic clearance approaching liver blood flow, suggesting a high hepatic extraction ratio, and a large volume of distribution at steady state. Computer simulations with this model suggested clinical advantages of sufentanil infusions compared to infusions of fentanyl or alfentantil when the rate of decrease from steady-state plasma concentrations is considered.

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