

Pharmacokinetics of Sufentanil in Patients Undergoing Abdominal Aortic Surgery

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The authors determined the pharmacokinetics of sufentanil, 12.5 $\mu\text{g} \cdot \text{kg}^{-1}$ iv in patients undergoing elective abdominal aortic surgery. The mean age (\pm SD) of the ten patients was 68.4 ± 7.9 yr; their mean weight was 74.4 ± 19.1 kg. Six patients underwent aortobifemoral grafting and four had abdominal aortic aneurysm repair. Serum sufentanil concentrations were determined in samples drawn at increasing intervals over a 24-h period. A three-compartment pharmacokinetic model was fit to the concentration *versus* time data. Total drug clearance was 15.0 ± 3.2 $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. The volume of distribution at steady-state ($V_{d,ss}$) was 8.7 ± 4.5 $\text{l} \cdot \text{kg}^{-1}$. The elimination half-time was 12.1 ± 5.8 h. Both the $V_{d,ss}$ and the elimination half-time were positively correlated with patient age. There were no significant correlations between the pharmacokinetic variables and the duration of aortic cross-clamping, the duration of surgery, or the rate or total volume of iv fluids given intraoperatively. In general surgical patients, the mean elimination half-time of sufentanil has been reported to be 2.7 h. When sufentanil is used in large doses as the primary anesthetic agent for patients undergoing abdominal aortic surgery, the long elimination half-time observed implies that recovery will take much longer than would have been anticipated from previously published pharmacokinetic data. (Key words: Anesthetics, intravenous; sufentanil. Pharmacokinetics: sufentanil. Surgery: abdominal aorta; vascular.)

PROVIDING ANESTHESIA with sufentanil is popular for patients having cardiovascular surgery because this technique is associated with hemodynamic stability and suppression of neuroendocrine responses to surgery.¹ Furthermore, a recent report suggests that, compared to isoflurane, sufentanil anesthesia is associated with a lower incidence of postoperative complications in patients undergoing abdominal or thoracoabdominal aortic surgery.²

Ideally, to achieve and maintain a desired drug concentration, intravenous anesthetics like sufentanil should be administered by continuous infusion based upon pharmacokinetic data and principles. However, the pharmacokinetics of sufentanil have not been determined in patients undergoing abdominal aortic surgery. Pharmacokinetic variables from other patient populations may not be applicable, because opiate disposition is altered in patients having abdominal aortic surgery.³ Therefore, we determined the pharmacokinetics of sufentanil 12.5 $\mu\text{g} \cdot \text{kg}^{-1}$ in this patient population.

Materials and Methods

After approval by the Human Subjects Committee, informed consent was obtained from each participant. Ten patients (eight men, two women) undergoing abdominal aortic surgery with infrarenal aortic cross-clamping were studied. Demographic information is shown in table 1.

The patients' regular medications were continued up to the time of surgery. Morphine 0.15 $\text{mg} \cdot \text{kg}^{-1}$ im and scopolamine 0.006 $\text{mg} \cdot \text{kg}^{-1}$ im were given 1 h prior to transfer to the operating room. Intravenous, radial arterial, and pulmonary arterial catheters were inserted before induction of anesthesia. Anesthesia was induced with sufentanil 7.5 $\mu\text{g} \cdot \text{kg}^{-1}$, infused at 2.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Metocurine 0.6 $\text{mg} \cdot \text{kg}^{-1}$ was given concomitantly for muscle relaxation. Ventilation was controlled manually, and the trachea was intubated 2 min after completion of the sufentanil infusion. A second dose of sufentanil 5.0 $\mu\text{g} \cdot \text{kg}^{-1}$ was infused at the same rate just prior to skin incision.

No additional anesthetics were given until either heart rate or mean arterial pressure increased to 120% of the value measured immediately after the second infusion. The sufentanil concentration at that time was calculated by interpolation between measured concentrations, providing an estimate of the concentration required to suppress hemodynamic responses to surgical stimulation. Subsequently, nitrous oxide, diazepam, or morphine were given at the discretion of the attending anesthesiologist. Small additional doses of metocurine and/or pancuronium were used as necessary. All patients received antibiotics for prophylaxis against infection, heparin, protamine, and vasoactive drugs if indicated. Intraoperatively, an autotransfusion device was used for salvage and rein-

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fusion of autologous blood supplemented by homologous packed red blood cells if necessary, plus sufficient crystalloid to maintain pulmonary artery wedge pressure near the control value.

Postoperatively, patients were given diazepam, morphine, and vasoactive drugs as indicated, as well as any medications required for their underlying medical conditions. Fluids were given as needed to maintain normal cardiac filling pressures and urine output. The lungs of all patients were ventilated overnight, and tracheal extubation occurred 16–23 h after induction of anesthesia.

Samples of arterial blood were drawn according to the following schedule: 1, 3, 5, 10, 15, 20, 30, 45, 60, and 90 min and 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16, 18, and 24 h after the end of the first infusion. The serum was separated and stored at -20°C .

ANALYTIC TECHNIQUES

Serum sufentanil concentrations were determined in triplicate by radioimmunoassay (RIA) kits (Janssen Life Sciences Products). Control samples were prepared by adding sufentanil solution $200\text{ ng}\cdot\text{ml}^{-1}$ to pooled blank plasma to produce final concentrations of 0.15, 0.40, 0.85, 1.40, 2.80, 4.80, and $8.20\text{ ng}\cdot\text{ml}^{-1}$. The patient and control samples were extracted by mixing either 0.5 ml plasma and 0.5 ml blank plasma (for lower concentrations) or 0.2 ml plasma and 0.8 ml blank plasma (for higher concentrations), with 0.05 ml 30% methanol/ H_2O and 0.5 ml 0.5 M NaOH. After vortexing, 5.0 ml heptane-isoamyl alcohol (98.5/1.5 v/v) was added and the tubes were placed on a rotary mixer for 10 min at 200 rpm. After centrifuging, the organic phase was removed and evaporated under nitrogen at 55°C . The residue was dissolved in 0.05 ml methanol, followed by addition of 0.5 ml phosphate buffer (0.05 M, pH 7.5 with 2% bovine albumin). The tubes were vortexed and then centrifuged. The supernatant was transferred to polypropylene tubes and vortexed after adding 0.05 ml ^3H -sufentanil, then vortexed again after adding 0.2 ml sufentanil antiserum. In the nonspecific binding tubes, 0.2 ml deionized water was substituted for the antiserum. After mixing for 4 h at 50 rpm, 0.2 ml of dextran-charcoal suspension was added, and the tubes were mixed for another 2 h. After centrifuging at 5000 g for 25 min, the supernatant was combined with 6.0 ml Pico-Fluor 30 (Canberra Packard, Canada) in 7-ml glass scintillation vials. The vials were counted for 10 min, with correction for color and chemical quenching by external standard ratio. Daily, standards were diluted according to the RIA kit instructions, then 0.05 ml of each standard was mixed with 1.0 ml blank plasma and 0.5 ml 0.5 M NaOH, and then extracted in the same fashion as the patient and control samples. The standard curves were analyzed by weighted linear regres-

TABLE 1. Demographic Data

Patient	Age (Years)	Sex	Weight (kg)	Operation	Associated Conditions
1	53.0	M	61.2	ABF	COPD
2	59.2	M	104.0	ABF	Peptic ulcer disease
3	65.7	F	43.0	AAA	IHD, hypertension, COPD
					trigeminal neuralgia
4	67.3	M	61.2	ABF	Hypertension
5	67.7	M	95.1	AAA	IHD
6	71.3	M	80.4	ABF	Permanent pacemaker
7	72.0	M	82.8	AAA	Hypertension, previous CABG
8	72.7	M	72.0	AAA	Hypertension, COPD
9	73.7	M	60.4	ABF	Hypertension, COPD
10	81.0	F	56.7	ABF	Hypertension

AAA = aortic aneurysm repair; ABF = aortobifemoral bypass; COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; CABG = coronary artery bypass grafts.

sion after logit transformation, and the concentration in the patient samples was determined from the regression line. The measured concentrations reported are the mean of each triplicate. The between-day coefficient of variation of the assay was 11.6% at $0.15\text{ ng}\cdot\text{ml}^{-1}$, 11.0% at $1.4\text{ ng}\cdot\text{ml}^{-1}$, and 3.3% at $8.2\text{ ng}\cdot\text{ml}^{-1}$.

Concentrations less than $0.1\text{ ng}\cdot\text{ml}^{-1}$ were measured in a total of 15 samples drawn between 14 and 24 h in six subjects. Because this is below our lowest concentration in our control samples, these data points were excluded from the pharmacokinetic analysis.

DATA ANALYSIS

Exponential equations based upon two- and three-compartment models and allowing for multiple infusions (see Appendix) were fit to the serum sufentanil concentration *versus* time data using the PCNONLIN nonlinear regression program.⁴ A weighting scheme of $1/[\text{predicted concentrations}]$ was used. The statistically preferred model was determined by the F-ratio test.⁵ Standard formulae were used to calculate drug clearances, the volume of central compartment (V_c), peripheral compartment volumes (V_2 and V_3), the volume of distribution at steady-state (V_{d_s}), and the distribution and elimination half-times.⁶ Linear regression was used to test for correlations between the derived pharmacokinetic variables and age, weight, duration of abdominal aortic cross-clamping (defined as the duration from placement of the proximal cross-clamp to removal to removal of all distal clamps), duration of surgery, and the rate and volume of iv fluids (crystalloid, colloid, and blood products) infused intra-

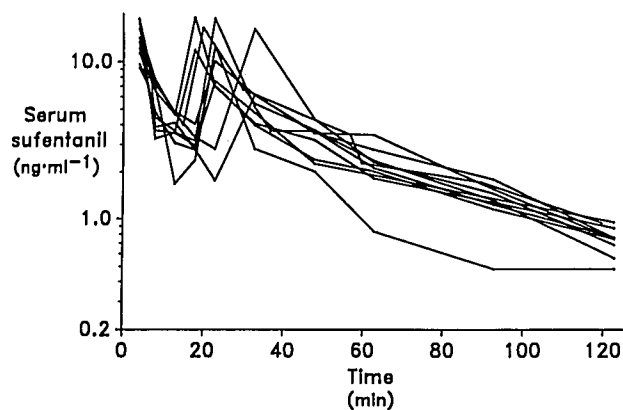


FIG. 1. A composite plot of the measured serum sufentanil concentrations versus time for the first 120 min after administration of the first dose of sufentanil. The peaks between 20 and 40 min are due to administration of the second dose of sufentanil.

operatively. Null hypotheses were rejected when P was less than 0.05.

Results

Composite plots of the measured serum sufentanil concentrations versus time are shown in figures 1 and 2. In all ten subjects, the three-compartment model described the concentration versus time data significantly better than did the two-compartment model. Total drug clearance ($\text{ml} \cdot \text{min}^{-1}$) was significantly correlated with body weight ($r = 0.73, P = 0.017$). The derived pharmacokinetic variables are listed in tables 2-4.

There were significant positive correlations between patient age and the $V_{d_{ss}}$ and elimination half-time (figs. 3, 4). Neither V_c nor total drug clearance were signifi-

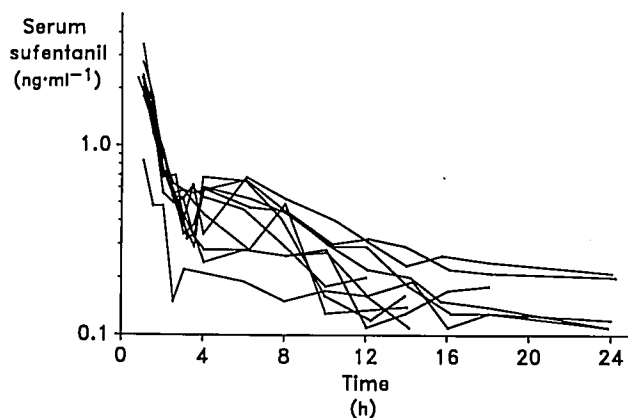


FIG. 2. A composite plot of the measured serum sufentanil concentrations versus time from 1 to 24 h after administration of the first dose of sufentanil. During the elimination phase, secondary peaks of the sufentanil concentration are evident in several patients.

TABLE 2. Half-times

Patient	Rapid Distribution Half-time (Min)	Slow Distribution Half-time (Min)	Elimination Half-time (h)
1	1.6	20.9	5.5
2	0.8	21.7	6.6
3	1.3	15.7	5.0
4	1.8	36.0	18.0
5	1.5	20.6	7.3
6	1.6	25.0	16.1
7	2.2	28.5	16.2
8	1.6	24.0	10.0
9	1.1	25.9	17.2
10	2.5	24.4	19.6
Mean	1.6	24.3	12.1
SD	0.5	5.4	5.8

cantly correlated with patient age. As well, there were no significant correlations between the duration of aortic cross-clamping (89 ± 37 min), the duration of surgery (227 ± 70 min), the rate of intraoperative iv fluid administration ($28.5 \pm 9.2 \text{ ml} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$), or the total volume of intraoperative iv fluids ($104 \pm 37 \text{ ml} \cdot \text{kg}^{-1}$).

Secondary peaks of the sufentanil concentration, defined as increases in the measured concentration of at least twice the coefficient of variation of the assay in two consecutive samples, were observed in six subjects (fig. 2). These peaks occurred in five patients 3-10 h after the initial dose, either late during the course of surgery (after vascular clamps had been removed), or after transfer of the patient to the intensive care unit, at which time the patients were beginning to move spontaneously as they recovered from the effects of anesthetic and neuromuscular blocking drugs. One patient did not awaken until 13 h after induction, and in this individual a secondary peak was observed 14-18 h after induction of anesthesia.

TABLE 3. Volumes of Distribution

Patient	Volumes of Distribution ($\text{l} \cdot \text{kg}^{-1}$)			
	V_c	V_2	V_3	$V_{d_{ss}}$
1	0.407	0.700	4.47	5.57
2	0.109	0.524	3.31	3.94
3	0.216	0.432	3.62	4.27
4	0.300	0.940	11.15	12.40
5	0.356	0.612	5.25	6.22
6	0.210	0.534	8.24	8.99
7	0.200	0.498	8.09	8.79
8	0.287	0.631	6.41	7.33
9	0.167	0.729	10.05	10.95
10	0.283	0.562	17.90	18.74
Mean	0.254	0.616	7.85	8.72
SD	0.090	0.146	4.42	4.47

V_c = volume of the central compartment; V_2 = volume of the rapidly equilibrating compartment; V_3 = volume of the slowly equilibrating compartment; $V_{d_{ss}}$ = volume of distribution at steady state.

TABLE 4. Clearances

Patient	Clearances (ml · min ⁻¹ · kg ⁻¹)		
	Total Drug Clearance	Rapid Intercompartmental Clearance	Slow Intercompartmental Clearance
1	19.4	93.3	21.3
2	14.4	65.0	10.4
3	17.7	58.8	17.7
4	14.8	68.1	14.6
5	15.2	84.9	21.2
6	10.1	52.1	15.4
7	13.2	32.0	10.5
8	14.4	72.0	16.6
9	11.0	66.6	19.5
10	19.6	28.5	23.6
Mean	15.0	62.1	17.1
SD	3.2	20.6	4.5

Rapid intercompartmental clearance = $V_c(K_{12}) = V_2(K_{21})$. Slow intercompartmental clearance = $V_c(K_{13}) = V_3(K_{31})$.

The serum sufentanil concentration at the time of hemodynamic response to surgical stimulation could not be estimated in two subjects. Patient 1 was given diazepam 5 mg iv at the time of tracheal intubation by the attending anesthesiologist, violating the protocol. Patient 8 became hypertensive during the second sufentanil infusion (prior to surgery) and required treatment with diazepam and sodium nitroprusside. In the remaining eight patients, hemodynamic responses to surgical stimulation occurred 61 ± 36 min after induction of anesthesia. At the time patients responded to surgical stimuli, the mean serum sufentanil concentration was 3.1 ± 1.6 ng · ml⁻¹ (range 0.6–4.9 ng · ml⁻¹). With one exception, the hemodynamic responses occurred during the intraabdominal phase of surgery. Patient 6 responded shortly after skin incision.

Discussion

There is very little information regarding sufentanil pharmacokinetics in humans. Bovill *et al.* administered sufentanil, $5 \mu\text{g} \cdot \text{kg}^{-1}$, to ten patients aged 22–64 yr undergoing general surgery.⁷ Plasma sufentanil concentrations were measured in samples drawn up to 8 h after sufentanil administration, and total drug clearance was determined to be $12.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, with a $V_{d_{ss}}$ of $1.7 \text{ l} \cdot \text{kg}^{-1}$, and an elimination half-time of 2.7 ± 0.4 h.

Total sufentanil clearance in our patients was $15.0 \pm 3.2 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, which is comparable to that reported by Bovill *et al.* However, the $V_{d_{ss}}$ was much larger in our patients undergoing abdominal aortic surgery, $8.7 \pm 4.5 \text{ l} \cdot \text{kg}^{-1}$, than in their patients undergoing general surgery. The large $V_{d_{ss}}$ accounts for the very long elimination half-time, 12.1 ± 5.8 h, that we observed.

Two important aspects of our study design differed from that of Bovill *et al.* First, they administered 5

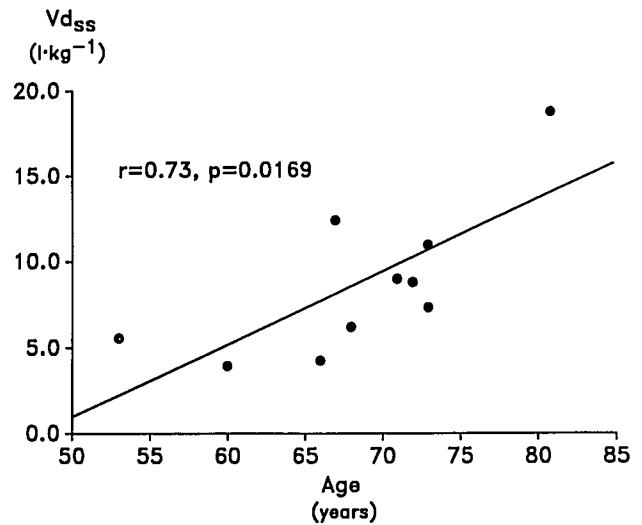


FIG. 3. Linear regression analysis of the volume of distribution at steady state ($V_{d_{ss}}$) versus patient age.

$\mu\text{g} \cdot \text{kg}^{-1}$ in a single dose, whereas we administered a total of $12.5 \mu\text{g} \cdot \text{kg}^{-1}$ in two doses. However, the dose regimen is exceedingly unlikely to have influenced pharmacokinetics because: 1) the total mass of drug administered was still small, 2) nonlinear, dose-dependent clearance is associated with low rates of drug clearance, rather than higher rates as we observed, and 3) we easily fit a linear pharmacokinetic model to the data. The second major difference is the duration of blood sampling. Bovill *et al.* sampled for 8 h, whereas we sampled for 24 h. The magnitude of the elimination half-time may be underestimated

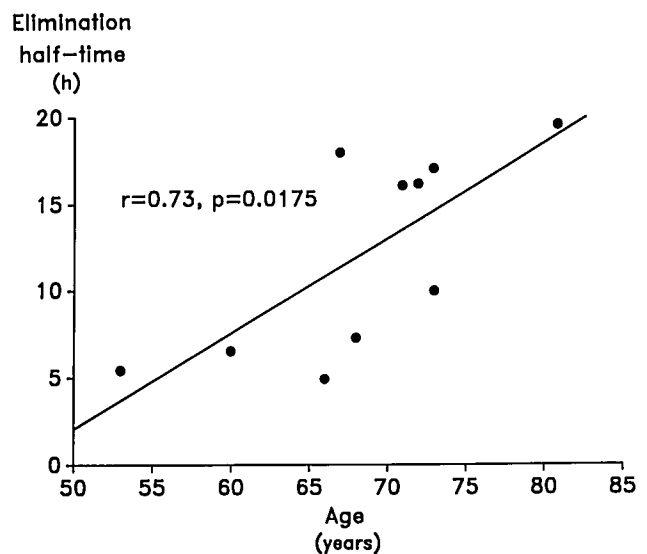


FIG. 4. Linear regression analysis of the elimination half-time versus patient age.

if sampling does not continue far enough into the elimination phase.⁸ This difference in study design could account, in part, for the longer elimination half-time observed in our patients.

Many factors could alter drug disposition in elderly patients undergoing abdominal aortic surgery, including intraoperative events such as the infusion of large volumes of iv fluids, and aortic cross-clamping.

Our patients ranged in age from 53 to 81 yr. Linear regression analysis indicated that the $V_{d_{ss}}$ of sufentanil increased significantly with increasing patient age ($r = 0.73$, $P = 0.0169$). Because sufentanil is lipophilic, the most likely explanation for this observation is the increase in the proportion of adipose tissue relative to total body weight that occurs with aging.⁹ As a result of the age-related increase in the $V_{d_{ss}}$, the elimination half-time increased with age ($r = 0.73$, $P = 0.0175$). The association of increased age with a larger $V_{d_{ss}}$ and a longer elimination half-time suggests that sufentanil may be eliminated more slowly in other elderly patients.

The routine use of an autotransfusion device to salvage, wash, and reinfuse blood lost during surgery is unlikely to have materially influenced the pharmacokinetics of sufentanil. Shanks *et al.* showed that the pharmacokinetics of d-tubocurarine were not affected by massive blood loss or autotransfusion.¹⁰ Neuromuscular blockers have much smaller volumes of distribution than sufentanil¹¹ and, consequently, a relatively greater amount of these drugs remains in the blood after distribution is completed. Therefore, if the pharmacokinetics of d-tubocurarine are unaffected by blood loss or autotransfusion, it is very unlikely that the disposition of a drug like sufentanil would be substantially altered by these factors.

Infrarenal aortic cross-clamping activates the renin-angiotension system.¹² This could aggravate the decrease in hepatic blood flow that occurs with intraabdominal surgery.^{13,14} However, we were unable to demonstrate significant correlations between the derived pharmacokinetic variables (total drug clearance, V_c , $V_{d_{ss}}$, and elimination half-time) and either the duration of aortic cross-clamping or the duration of surgery.

Our patients received large volumes of crystalloid intraoperatively. Hemodilution decreases drug binding to plasma proteins.¹⁵ The resulting increase in the unbound sufentanil fraction will tend to increase the $V_{d_{ss}}$.¹⁵ The large volume of fluids infused could have contributed to the large $V_{d_{ss}}$ observed. Although the pharmacokinetic variables did not correlate significantly with either the volume or rate of iv fluids administered intraoperatively, this does not mean that these intraoperative factors are unimportant, because our study group of patients was small and homogeneous, and fluid therapy was similar in all patients. We did not attempt to correlate blood loss with the pharmacokinetic variables, because the use of

autotransfusion precluded precise measurement of blood loss.

We observed secondary peaks of the measured sufentanil concentration during the elimination phase in several patients (fig. 2). This phenomenon has also been reported with fentanyl,¹⁶⁻²⁰ including patients undergoing abdominal aortic surgery.³ It has been suggested that the secondary peaks of the fentanyl concentration are due to elution of drug from muscle during emergence, when spontaneous movement increases muscle blood flow.^{20,21} The timing of the secondary peaks in our patients suggests that a similar phenomenon may occur with sufentanil. Such secondary peaks of the drug concentration could account for recurrent postoperative respiratory depression occasionally seen after apparent recovery from sufentanil.²²⁻²⁴

The occurrence of secondary peaks suggests that intercompartmental clearances of sufentanil were not constant throughout the study. The magnitude of other parameters, such as the volume of distribution or total drug clearance, may also have fluctuated over the study period. Compartmental pharmacokinetic models are based on the assumption that the parameters are constant, and, therefore, only provide time-weighted average estimates of clearances and volumes of distribution over the study period. In spite of this inherent limitation, the concentrations predicted by the three-compartment model adequately approximated the measured concentrations.

The serum sufentanil concentration at which patients required additional drugs to control hemodynamic responses to surgical stimulation was highly variable, ranging from 0.6 to 4.9 ng · ml⁻¹ (mean 3.1 ng · ml⁻¹). These hemodynamic responses occurred after skin incision or during the intraabdominal phase of surgery. The opiate concentration required to prevent responses varies according to the intensity of the surgical stimuli,²⁵ which may account for some of the variability. In our previous study of high-dose fentanyl in patients having abdominal aortic surgery,²⁶ hemodynamic responses occurred at a mean fentanyl concentration of 18.5 ± 5.6 ng · ml⁻¹. These data suggest that equipotent plasma concentrations of sufentanil and fentanyl differ sixfold.

We previously demonstrated a long elimination half-time for fentanyl (8.7 ± 2.5 h) in patients undergoing abdominal aortic surgery,³ compared with reported elimination half-times in patients undergoing general surgery.²¹ This was primarily due to a large $V_{d_{ss}}$ of fentanyl, although total drug clearance was somewhat slower than that reported in normal volunteers or general surgical patients.²¹ In our patients undergoing abdominal aortic surgery, the $V_{d_{ss}}$ of sufentanil is even greater than the $V_{d_{ss}}$ of fentanyl, 8.7 ± 4.5 versus 5.4 ± 1.9 l · kg⁻¹, respectively ($P < 0.05$ by *t* test).³ The larger volume of distribution of sufentanil is compatible with the fact that

sufentanil is approximately twice as lipid soluble as fentanyl.²⁷ These results differ from those of Bovill *et al.*, whose data suggest that the $V_{d_{ss}}$ of sufentanil is slightly smaller than the $V_{d_{ss}}$ of fentanyl.^{7,21} The differences in study design and patient population discussed above presumably account for these conflicting results.

In summary, we found a very long elimination half-time of sufentanil (12.1 ± 5.8 h) in patients undergoing abdominal aortic surgery. Clearance of sufentanil in our patients was similar to values reported for patients undergoing general surgery.⁷ The long elimination half-time in our patients was due to a large $V_{d_{ss}}$.

Our results have implications for clinical practice. If sufentanil is used as the primary anesthetic agent for patients undergoing abdominal aortic surgery, recovery will take much longer than would have been anticipated from previously published pharmacokinetic studies, especially in older patients.

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Appendix

The following formula, based on the principle of superposition,²⁸ was used to model the concentration *versus* time data by nonlinear regression:

$$C(t) = \sum_{j=1}^n \left[\sum_{i=1}^c A_i k_j (e^{a_i(t-t_j)} - 1) (e^{-a_i(t-t_j)}) / (a_i(D)) \right]$$

where $C(t)$ = plasma concentration at time t ; i = number of exponential terms or compartments; j = number of infusions up to time t ; A_i = intercept of the i th term at $t = 0$; a_i = hybrid rate constant of the i th term; k_j = rate of the j th infusion; t = time from the start of the first infusion; t_j = time of the start of the j th infusion; t_d_j = lesser of: $t - t_j$ or duration of the j th infusion; and D = total dose.