Alfentanil pharmacokinetics in patients undergoing abdominal aortic surgery

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The pharmacokinetics of alfentanil, 300 $\mu g \cdot kg^{-1}$ IV, were determined in patients undergoing elective abdominal aortic reconstruction. The mean age (± SD) of the patients was 64.3 ± 7.4 yr; their mean weight was 74.7 ± 13.8 kg. Five patients underwent aneurysm repair and six had aortobifemoral grafting. Serum alfentanil concentrations were measured by gas-liquid chromatography in samples drawn at increasing intervals over a 24-hr period. A three-compartment model was fitted to the concentration versus time data. The volume of the central compartment and the volume of distribution at steady state (Vd_{ss}) were 0.044 ± 0.022 and 0.63 ± 0.32 $L \cdot kg^{-1}$, respectively. Total drug clearance was 6.4 = 1.9 $ml \cdot min^{-1} \cdot kg^{-1}$. The elimination half-time was 3.7 ± 2.6 hr. Patient age was positively correlated with both Vd_{ss} and elimination half-time. 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 infused intraoperatively. In general surgical patients, the elimination half-time of alfentanil has been reported to be 1.2–2.0 hr. Although the elimination half-time of alfentanil was longer in patients undergoing abdominal aortic surgery, alfentanil was eliminated much faster than either fentanyl or sufentanil in this patient population.

Nous avons tracé le profil pharmacocinétique d'une dose intraveineuse de 300 $\mu g \cdot kg^{-1}$ d'alfentanil lors de reconstructions électives de l'aorte. Cinq patients subirent une résection d'anévrysme et six autres, un pontage aorto-bifémoral. Ils avaient en moyenne 64,3 ± 7,4 ans et pesaient 74,7 ± 13,8 kg. On mesura les concentrations sériques d'alfentanil par chromatographie gaz-liquide sur des échantillons prélevés à intervalles croissants pendant 24 h. L'évolution temporelle des concentrations était celle d'un modèle pharmacocinétique tricompartimental. Le compartiment central avait un volume de 0,044 ± 0,022 $L \cdot kg^{-1}$ et le volume de distribution à l'équilibre (Vd_{ss}) était de 0,63 ± 0,32 $L \cdot kg^{-1}$; la clairance était de 6,4 ± 1,9 $ml \cdot min^{-1} \cdot kg^{-1}$ et la demie-vie d'élimination, 3,7 ± 2,6 h. Il y avait une corrélation positive entre l'âge du patient, le Vd_{ss} et la demie-vie. Les variables pharmacocinétiques étaient toutefois indépendantes de la durée du clampage aortique et de l'intervention, de même que du débit et du volume des liquides perfusés par voie veineuse pendant l'opération. Même si elle s'est avérée plus longue que celle de 1,2 à 2 h observée en chirurgie générale, la demie-vie d'élimination de l'alfentanil est beaucoup plus courte que celles du fentanyl et du sufentanil lors de chirurgie aortique.

Key words
ANAESTHETICS, INTRAVENOUS: alfentanil;
PHARMACOKINETICS: alfentanil;
SURGERY: abdominal aorta; vascular.

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Fentanyl and sufentanil are eliminated very slowly in patients undergoing abdominal aortic surgery.[1,2] Consequently, large doses of either of these opioids may cause prolonged postoperative respiratory depression in patients undergoing aortic surgery. In general surgery patients, alfentanil is eliminated much more rapidly than either fentanyl or sufentanil,[3] suggesting that, after large doses, recovery of respiratory drive might be more rapid after alfentanil. As a prerequisite to designing continuous infusion regimens, we determined the pharmacokinetics of alfentanil, 300 $\mu g \cdot kg^{-1}$, in patients undergoing abdominal aortic surgery.

Methods

After approval by the Human Subjects Committee, informed consent was obtained from each participant. Nine men and two women undergoing elective abdominal aortic surgery with infrarenal aortic cross-clamping were studied. Demographic data are shown in Table I.

The patients' regular medications were continued up to

TABLE I Demographic data

Patient	*Age (yr)*	*Weight (kg)*	*Operation*	*Associated conditions*
1	51.7	71.2	ABF	
2	53.4	61.0	ABF	COPD, hypertension, IHD
3	60.0	69.7	ABF	Type II diabetes, gout, hypertension, IHD, previous CABG
4	61.2	97.8	AAA	IHD, previous CABG
5	64.6	86.0	AAA	Histiocytic lymphoma in remission
6	64.7	83.6	AAA	COPD, hypertension, IHD, previous CABG
7	66.3	83.6	AAA	Type II diabetes, mild uraemia, hypertension, COPD
8	66.9	79.1	AAA	
9	69.0	67.6	ABF	Hypertension, IHD
10	72.7	46.4	ABF	Hypertension, IHD, previous stroke
11	76.3	76.0	ABF	
Mean	64.3	74.7		
SD	7.4	13.8		

Patients 9 and 10 were females; AAA = aortic aneurysm repair; ABF = aortobifemoral bypass; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; IHD = ischaemic heart disease.

the time of surgery. Morphine 0.15 $mg \cdot kg^{-1}$ IM and scopolamine 0.006 $mg \cdot kg^{-1}$ IM were given one hour before transfer to the operating room. Intravenous, radial arterial, and pulmonary arterial catheters were inserted before induction of anaesthesia. Anaesthesia was induced with alfentanil, 175 $\mu g \cdot kg^{-1}$ infused at 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Metocurine 0.11 $mg \cdot kg^{-1}$ and pancuronium 0.027 $mg \cdot kg^{-1}$ were given concomitantly. After tracheal intubation, mechanical ventilation was begun. To increase the plasma concentration of alfentanil, a second dose, 125 $\mu g \cdot kg^{-1}$, was infused at the same rate just before skin incision. Seven patients received nitrous oxide, 50 to 70 per cent inspired, during the interval between the alfentanil infusions.

No other anaesthetics were given until either heart rate or mean arterial pressure increased to 120 per cent of the value measured prior to the second infusion. Subsequently, diazepam, morphine, isoflurane or nitrous oxide were given at the discretion of the attending anaesthetist. Additional neuromuscular blocking drugs were given as needed. All patients received antibiotics for prophylaxis against infection, heparin, protamine, and vasoactive drugs, if indicated. An autotransfusion device was used during surgery to salvage and reinfuse autologous red blood cells. This was supplemented with homologous packed red blood cells if necessary, plus enough crystalloid to maintain pulmonary artery wedge pressure near the control value.

During the first 24 hr postoperatively, patients were given diazepam, morphine and vasoactive drugs as needed, as well as any medications required for their chronic medical conditions. Intravenous fluids were given to maintain cardiac filling pressures and adequate urine output. In all patients the lungs were electively ventilated postoperatively, and the tracheas were extubated 12–24 hr after induction of anaesthesia.

Arterial blood was sampled according to the following schedule: 4, 6, 8, 13, 18, 23, 33, 48 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16, 20, 24 hr after the start of the first alfentanil infusion. The serum was separated and stored at −20° C.

Analytical techniques

Serum alfentanil concentrations were measured by gas-liquid chromatography with a nitrogen-phosphorus detector, using sufentanil as the internal standard.[1] The coefficient of variation of the assay was nine per cent over the concentration range from 2 to 2000 $ng \cdot ml^{-1}$.

The measured serum alfentanil concentrations decreased to less than 1 $ng \cdot ml^{-1}$ in all subjects within 20 hr. Measured alfentanil concentrations less than 1 $ng \cdot ml^{-1}$ were excluded from the pharmacokinetic analyses.

Data analysis

Exponential equations based upon two- and three-compartment models and allowing for multiple infusions[2] were fit to the serum concentration versus time data using the PCNONLIN nonlinear regression program.[4] A weighting scheme of 1/[predicted concentrations] was used. For each subject, the preferred model was determined using the F-ratio test.[5] Drug clearances, the volume of the central compartment (V_c), peripheral compartment volumes (V_2 and V_3), the volume of distribution at steady state (Vd_{ss}), and the distribution and

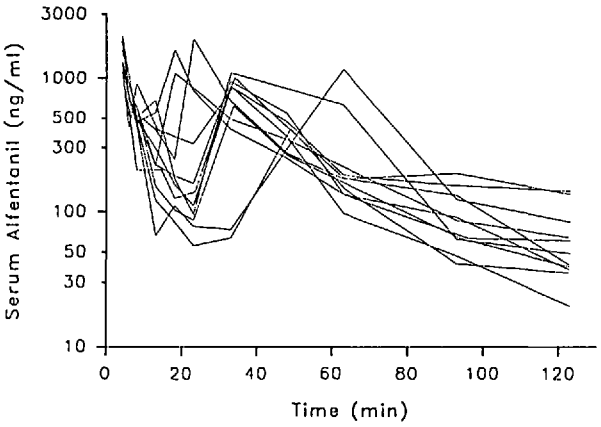

FIGURE 1 A composite graph of the measured serum alfentanil concentrations versus time for the first 120 min after infusion of the first dose. The peaks between 20 and 70 min reflect the infusion of the second dose of alfentanil.

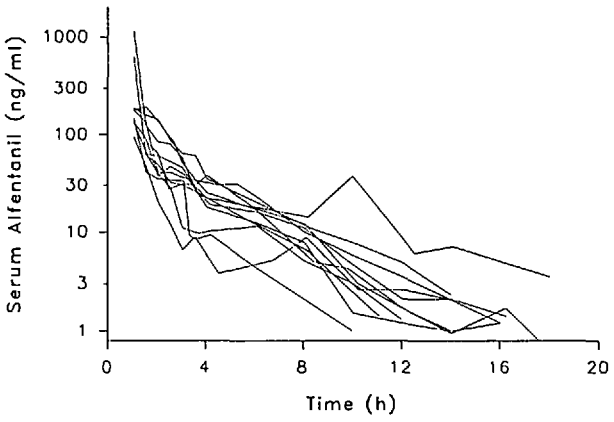

FIGURE 2 A composite graph of the measured serum alfentanil concentrations versus time from 1 to 20 hr after infusion of the first dose. During the elimination phase, secondary peaks are evident in several subjects.

elimination half-times were calculated with standard formulae.[6]

Linear regression, and exponential regression where applicable, were used to test for correlations between the derived pharmacokinetic variables and age, weight, the duration of abdominal aortic cross-clamping (defined as the time from placement of the proximal cross-clamp to removal of all distal vascular clamps), and the rate and total volume of IV fluids (crystalloid, colloid, and blood products) given during surgery. Null hypotheses were rejected when P was less than 0.05.

Results

Composite graphs of the measured serum alfentanil concentrations versus time are shown in Figures 1 and 2. In ten of the 11 subjects, the three-compartment model described the concentration versus time data significantly better than did the two-compartment model ($P < 0.05$). For consistency, the pharmacokinetic variables from the three-compartment model are presented for all 11 subjects. Linear regression demonstrated that the total volume of the central compartment (1) was positively correlated with body weight ($r = 0.60$, $P < 0.05$), as was total drug clearance expressed as $ml \cdot min^{-1}$ ($r = 0.68$, $P < 0.05$). The derived pharmacokinetic variables are listed in Tables II–IV, with the volumes and clearances normalized for body weight.

There were significant positive correlations between

TABLE II Half-times

Patient	*Rapid distribution half-time (min)*	*Slow distribution half-time (min)*	*Elimination half-time (hr)*
1	0.3	4.5	1.2
2	0.9	12.9	1.9
3	0.5	12.4	1.9
4	2.2	34.6	4.1
5	2.0	23.3	2.9
6	0.8	23.7	2.9
7	1.7	72.6	1.9
8	1.5	38.6	2.3
9	0.9	23.2	3.9
10	1.5	32.5	7.6
11	1.6	24.3	9.5
Mean	1.3	27.5	3.7
SD	0.6	18.1	2.6

TABLE III Volumes of distribution

	Volumes of distribution ($L \cdot kg^{-1}$)			
Patient	V_c	V_2	V_3	Vd_{ss}
1	0.013	0.039	0.270	0.322
2	0.029	0.082	0.275	0.386
3	0.028	0.108	0.313	0.449
4	0.070	0.243	0.470	0.783
5	0.071	0.147	0.387	0.605
6	0.022	0.134	0.256	0.412
7	0.055	0.583	0.069	0.707
8	0.040	0.241	0.098	0.378
9	0.028	0.139	0.450	0.618
10	0.049	0.161	0.634	0.844
11	0.075	0.206	1.163	1.444
Mean	0.044	0.189	0.399	0.632
SD	0.022	0.145	0.301	0.322

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

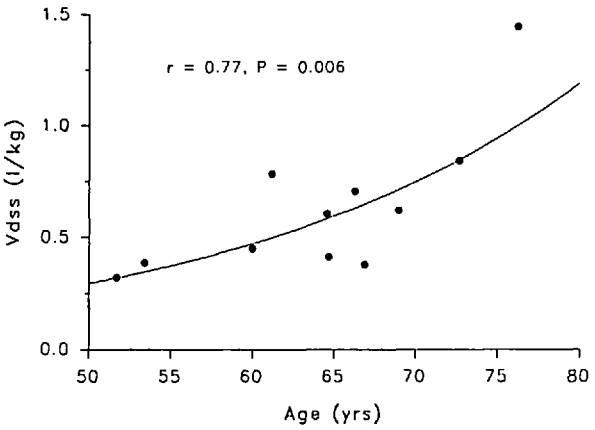

FIGURE 3 Exponential regression analysis of the volume of distribution at steady state: (Vd_{ss}) versus patient age: $Vd_{ss} = 0.029\ e^{0.046(age)}$.

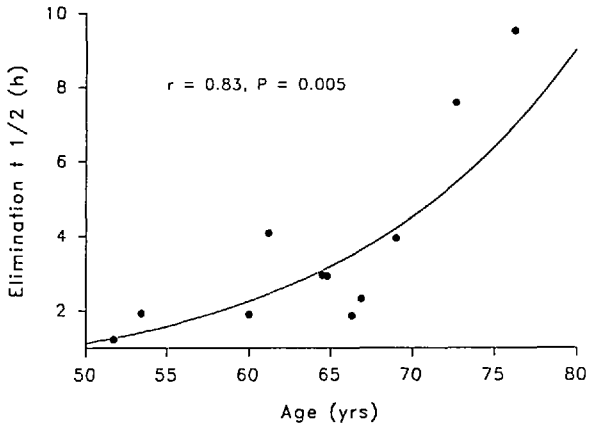

FIGURE 4 Exponential regression analysis of the elimination half-time versus patient age: half-time = $0.035\ e^{0.070(age)}$.

patient age and the Vd_{ss} and the elimination half-time (Figures 3 and 4). Neither total drug clearance nor the V_c were correlated with age. Also, there were no significant correlations between any of the calculated pharmacokinetic variables and the duration of aortic cross-clamping (91 ± 32 min), the duration of surgery (223 ± 50 min), the rate of intraoperative fluid administration (26.6 ± 5.8 $ml \cdot hr^{-1} \cdot kg^{-1}$), or the total volume of fluids infused during surgery (96.3 ± 17.1 $ml \cdot kg^{-1}$).

In three patients, secondary peaks of the measured alfentanil concentration, defined as an increase of at least twice the coefficient of variation of the assay, were observed between 7 and 16 hr after administration of alfentanil (Figure 2).

All patients required additional anaesthetic agents (N_2O, isoflurane, morphine, or diazepam) within a few minutes of the skin incision.

TABLE IV Clearances

	Clearances ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Patients	*Total drug clearance*	*Rapid intercompartmental clearance*	*Slow intercompartmental clearance*
1	4.9	15.1	6.1
2	5.9	11.3	2.4
3	4.8	26.1	3.7
4	9.2	9.7	1.6
5	6.5	11.8	2.1
6	5.0	11.3	1.3
7	8.2	12.7	0.5
8	8.1	9.2	0.5
9	4.8	12.7	1.9
10	4.2	14.0	1.3
11	9.2	17.9	1.7
Mean	6.4	13.8	2.1
SD	1.9	4.8	1.6

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

Discussion

The pharmacokinetic variables of alfentanil in adult surgical patients have been extensively investigated.[7-20] In these studies, mean estimates of the elimination half-time range from 1.2 to 2.0 hr. Mean values for clearance range from 3.1 to 7.9 $ml \cdot min^{-1} \cdot kg^{-1}$, and mean Vd_{ss} range from 0.28 to 0.54 $L \cdot kg^{-1}$.

The elimination half-time of alfentanil in our patients was 3.7 ± 2.6 hr. Total alfentanil clearance in our patients, 6.4 ± 1.9 $ml \cdot min^{-1} \cdot kg^{-1}$, is within the range of previously reported values. Therefore, the larger Vd_{ss}, 0.632 ± 0.322 $L \cdot kg^{-1}$ accounts for longer elimination half-time that we observed.

Our study differed in two major aspects from other studies of alfentanil pharmacokinetics – the total dose administered and the duration of blood sampling. The total dose of alfentanil was 300 $\mu g \cdot kg^{-1}$, whereas other investigators used from 20 to 120 $\mu g \cdot kg^{-1}$.[17-18] However, the longer elimination half-time does not appear to be due to nonlinear, dose-dependent clearance because: (1) nonlinear clearance only occurs with very low clearance rates, and (2) mean total drug clearance in our patients was within the range of previously reported values. Furthermore, in two other studies[19,20] in which total doses of 240 and 350 $\mu g \cdot kg^{-1}$ were administered, the derived pharmacokinetic variables were similar to those obtained in studies in which lower doses were used.[7-18] Other investigators gave single doses or contin-

uous infusions of alfentanil. However, differences in the mode of administration cannot account for differences in the derived pharmacokinetic variables, because, with first-order pharmacokinetics, clearances and volumes of distribution are independent of the dose and mode of administration.

In previous studies of alfentanil pharmacokinetics, blood samples have generally been drawn for eight hours or less. We drew blood samples for up to 24 hr after injection, and we were able to measure alfentanil concentrations until they were two orders of magnitude below therapeutic levels.[21] The elimination half-time may be underestimated if measurement of drug concentrations is not continued well into the elimination phase.[22] As well, in most of the previous reports of alfentanil pharmacokinetics, a two-compartment model was used.[7,10–14,16,18–20] For any set of data, the elimination half-time estimated with a two-compartment model will be shorter than that estimated by a three-compartment model. These differences in study design and data analysis could account, at least partly, for the longer elimination half-time observed in our patients.

Drug disposition could be affected by many factors in elderly patients undergoing abdominal aortic reconstructive surgery, including the duration of surgery, intraoperative events such as aortic cross-clamping and unclamping, and infusion of large volumes of crystalloid.

Our patients' ages ranged from 53 to 76 yr. Exponential regression demonstrated that the Vd_{ss} of alfentanil increased with increasing patient age ($r = 0.77$, $P < 0.01$). This observation is consistent with two other studies that have examined the effect of age on alfentanil kinetics. Meistelman *et al.* demonstrated that the Vd_{ss} of alfentanil, normalized for weight, was smaller in children aged four to eight years than in adults ranging in age from 27 to 35 yr.[16] In a population pharmacokinetic analysis, Maitre *et al.* showed that k_{31} decreased linearly with age in patients over 40 yr old.[15] Because they found no age-related changes in the V_c or k_{13}, a decrease in k_{31} must produce a proportionate increase of the V_3, which equates to an increased Vd_{ss}. These observations are likely due to the increase in the proportion of adipose tissue that occurs with aging.[23] In our patients, the age-related increase of the Vd_{ss} resulted in a similar positive correlation between age and elimination half-time ($r = 0.83$, $P = 0.005$).

Aortic cross-clamping and subsequent unclamping produces haemodynamic changes that could alter drug distribution and elimination. However, there were no significant correlations between the derived pharmacokinetic variables (V_c, Vd_{ss}, total drug clearance, and elimination half-time) and either the duration of aortic cross-clamping or the duration of surgery.

Large volumes of crystalloid were infused intraoperatively. Haemodilution decreases drug binding to plasma proteins, and the resulting increase of the unbound drug fraction tends to increase the Vd_{ss}.[24] The large volumes of fluids infused could have contributed to the large Vd_{ss} of alfentanil in our patients. Although none of the pharmacokinetic variables were correlated with either the rate or volume of fluids infused during surgery, we cannot conclude that these factors are unimportant because we studied a small, homogeneous group, and fluid therapy was similar for all patients. The use of intraoperative autotransfusion precluded precise measurement of blood loss, so we could not test for correlations between the pharmacokinetic variables and blood loss.

Using an autotransfusion device to salvage, wash and reinfuse blood lost during surgery potentially provides an artificial pathway for drug clearance. However, this is not likely to have affected our results. The pharmacokinetics of d-tubocurarine are not affected by either massive blood loss or autotransfusion.[25] Alfentanil has a slightly larger volume of distribution than d-tubocurarine.[25] Consequently, a smaller fraction of the amount of alfentanil in the body remains in the blood after distribution is completed. Therefore, if the pharmacokinetics of d-tubocurarine are not affected by blood loss or autotransfusion, it is unlikely that the disposition of alfentanil would be materially altered by either of these factors. As well, we did not observe an unusually high value for total drug clearance, which would occur if there was significant clearance of alfentanil by artificial routes.

In several patients, secondary peaks of the alfentanil concentration occurred during the elimination phase (Figure 2). This phenomenon has also been observed in patients given fentanyl or sufentanil, including patients undergoing abdominal aortic surgery.[1,2,26–29] We studied a twelfth patient in whom the alfentanil concentrations increased eight-fold (from 20 $ng \cdot ml^{-1}$ to 175 $ng \cdot ml^{-1}$) at the time of aortic unclamping. This made it impossible to fit a linear model to those data with adequate precision, and for that reason the pharmacokinetic variables from that patient have not been reported. It has been hypothesized that the secondary peaks of the fentanyl concentration are due to elution of drug from skeletal muscle during emergence from anaesthesia, as a result of spontaneous movement and increased muscle blood flow.[3,26] The timing of the secondary peaks, and the large increase in alfentanil concentrations associated with reperfusion of the lower extremities in one patient suggests that a similar phenomenon may occur with alfentanil. Secondary peaks of the alfentanil concentration could be responsible for recurrent respiratory depression and unconsciousness that is occasionally observed after apparent recovery from alfentanil.[30–32]

By giving a second dose of alfentanil just before skin

incision, we had hoped to be able to estimate the alfentanil concentration required to prevent haemodynamic responses to surgical stimulation. However, all patients required additional anaesthetics within a few minutes of the start of surgery. Therefore, the alfentanil concentrations measured at that time (Figure 1, 300–1000 ng · ml^{-1}, 40 to 60 min) did not prevent haemodynamic responses to surgery. These results are consistent with those obtained in a study of the use of alfentanil as a primary anaesthetic in patients undergoing coronary artery surgery.[33] In the doses used, alfentanil must be supplemented with other intravenous or inhalational anaesthetics. Also, administering alfentanil by continuous infusion would attenuate the rapid decreases in concentration observed after the loading and supplemental doses (Figure 1).

The results of this study are consistent with our previous studies of the pharmacokinetics of fentanyl and sufentanil in patients undergoing abdominal aortic surgery.[1,2] The elimination half-time of all three opioids is longer in patients undergoing aortic reconstruction than in general surgical patients. For all three drugs, this is primarily due to a larger volume of distribution, although clearance of fentanyl may be slightly lower in patients undergoing abdominal aortic surgery.[1,3]

All three opioids are highly bound to plasma proteins (84 to 92 per cent).[34] Under these circumstances, one would predict that differences in the volumes of distribution will reflect differences in lipid solubility, and the results of our studies confirm this. Alfentanil has the lowest octanol:water partition coefficient[33] and the smallest Vd_{ss}. Sufentanil is the most lipophilic and has the largest Vd_{ss}, and fentanyl is intermediate with regard to both properties.

In patients undergoing coronary artery surgery, the elimination half-time of alfentanil averages 5.1 hr.[35] Unfortunately, the physiological perturbations resulting from cardiopulmonary bypass precluded full pharmacokinetic analysis in this study. The relative contributions of decreased clearance and increased volume of distribution in producing a longer elimination half-time could not be determined from the data.

In summary, we found a long elimination half-time for alfentanil, 3.7± 2.6 hr, in patients undergoing abdominal aortic surgery. Clearance of alfentanil was similar to values reported for patients undergoing general surgery. The longer elimination half-time in our patients was due to a larger Vd_{ss}. If alfentanil is used in large doses as a primary anaesthetic agent for patients undergoing abdominal aortic surgery, recovery will take longer than would have been predicted from previously published pharmacokinetic studies, especially in older patients. However, alfentanil has the smallest volume of distribution, and thus is still eliminated much faster than either fentanyl or sufentanil in these patients. These pharmacokinetic differences should be considered in selecting the opioid for a specific situation.

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