

The Pharmacokinetics of Alfentanil in Children

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The pharmacokinetics of alfentanil were studied in 18 children (3 months to 14 yr of age) undergoing surgery. Alfentanil was administered as a 30-s infusion of either 50 or 120 $\mu\text{g} \cdot \text{kg}^{-1}$. Pharmacokinetic values were independent of dose. There was no correlation between V_{dss} (Volume of distribution at a steady state, measured as $\text{l} \cdot \text{kg}^{-1}$) and age or weight, and there was a weak correlation between clearance and age ($r = 0.51$, $P < 0.05$). V_{dss} and elimination $t_{1/2}$ were not different in infants less than 1 yr of age when compared to older children. The mean value of V_{dss} was 0.419 (SE .028) $\text{l} \cdot \text{kg}^{-1}$ for the whole group, and elimination $t_{1/2}$ was 76.3 (SE 6.5) min. The clearance rate [$\text{TBC} = 7.9$ (SE 0.41) $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$] was within the range of values previously determined in adult studies. From these data, it would appear that, although there may be differences in the disposition kinetics between children aged 3 months to 14 yr and those measured in adults in some studies by other investigators, age-related differences within this group were not demonstrable. (Key words: Anesthesia: pediatric. Anesthetics, intravenous: alfentanil. Pharmacokinetics: alfentanil.)

ALFENTANIL IS PHARMACOLOGICALLY and chemically related to fentanyl, but has a more rapid onset, and a much shorter duration, of action.^{1,2} The drug has a lower lipid solubility than fentanyl, is highly bound to plasma proteins (above 90%), and is rapidly eliminated by the liver with less than 1% being excreted unchanged in the urine.³ A short-acting drug such as alfentanil has obvious advantages in pediatric anesthesia, in that minimal accumulation, cardiovascular stability, and minimal postoperative side effects may provide a more predictable narcotic-based anesthetic for a variety of procedures.

There is, at present, little information regarding the pharmacokinetics of alfentanil in young children. The present study was undertaken to determine whether there are age-related differences in the disposition kinetics of alfentanil in children aged 3 months to 14 yr,

to determine whether there are dose-dependent pharmacokinetics, and to assess the cardiovascular effects of administration of this drug in anesthesia for children when combined with pancuronium.

Methods

This study was approved by the Joint Committee on Medical Bioethics of the University of Calgary and the Committee for Human Research at the Alberta Children's Hospital. Informed consent for inclusion of the children in the study was obtained from all parents.

Eighteen patients, divided into three groups, were studied. All patients were classified as ASA physical status I. Details of the patients and of the operative procedures are given in table 1. Group I ($n = 5$) were aged 3-12 months and group II ($n = 8$) aged 12 months to 14 yr; both groups received alfentanil 50 $\mu\text{g} \cdot \text{kg}^{-1}$. Group III patients, aged 14 months to 14 yr, received 120 $\mu\text{g} \cdot \text{kg}^{-1}$. Patients in group I were selected sequentially as they presented for surgery. Patients in groups II and III were designated for dose selection according to random assignment. With no premedication, patients received an inhalation induction of anesthesia with nitrous oxide in oxygen and halothane (1-3%), followed by a bolus of pancuronium 0.1 $\text{mg} \cdot \text{kg}^{-1}$. After endotracheal intubation, the lungs were mechanically ventilated with nitrous oxide/oxygen ($\text{FI}_{\text{O}_2} = 0.3$) and anesthesia was maintained with halothane 0.5% inspired concentration (end tidal halothane concentration was not measured.) A separate peripheral intravenous cannula was established for blood sampling or an arterial cannula was inserted if clinically required. A pre-alfentanil blood sample was obtained. Before the start of the operation, a single intravenous infusion of alfentanil was given (50 or 120 $\mu\text{g} \cdot \text{kg}^{-1}$) over 30 s. Throughout the operation, the electrocardiogram was monitored and blood pressure recorded using a Dinamap® recorder cycling every 3 min. Immediately after administration of the alfentanil, the halothane was discontinued and only started again at 0.5% inspired concentration when the anesthesiologist considered it necessary based upon the patient's cardiovascular response to the surgical stimulus, as manifested by tachycardia or hypertension.

Over the next 6 h following the administration of alfentanil, 14 blood samples were drawn and the plasma was separated immediately and stored at -18°C until

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assayed. Sampling times were 1, 2, 3, 5, 10, 15, 30, 45, and 60 min, and thereafter every hour for a total of 6 h after the administration of alfentanil. During the operation, a maintenance infusion of commercially prepared 3.3% dextrose and 0.3% saline was given.

Alfentanil plasma concentration was determined by radioimmunoassay technique similar to that employed for fentanyl, but using antiserum to alfentanil obtained from rabbits. The details of the radioimmunoassay (RIA) have been described by Michiels *et al.*⁴ Counts for each sample were determined using a Packard BPLD liquid scintillation counter, correcting for colour and chemical quenching on a sample-to-sample basis, done by External Standard Ratio. The RIA technique is specific for alfentanil with no cross-reactivity between alfentanil and any of its metabolites or any other opiate or anesthetic agent. The alfentanil concentration in the plasma samples was determined in triplicate. The accuracy and reproducibility of the assay were calculated by determining the alfentanil concentration in seven plasma samples spiked with alfentanil, in the concentration range of 0.2 nanogram \cdot ml⁻¹ to 600 nanogram \cdot ml⁻¹ (where plasma concentrations were out of this range, samples were diluted with plasma to bring them within this range). The measured alfentanil concentration was within 6% of the calculated concentration for all samples, with a coefficient of variation of 4% or less (where $n = 25$).

The plasma alfentanil concentration-time data from each patient was best fitted to a two-compartment open model using the Non-Lin computer program with a correction for infusion time of 30 s. Initial estimates of pharmacokinetic values were calculated using the curve-stripping program as described by Naizi⁵ on a Hewlett Packard[®] calculator. Weighting was performed by the inverse square of the predicted plasma concentration. Total body clearance (TBC) was calculated as $\text{Dose}/\text{AUC}_{0 \rightarrow \infty}$, where AUC = area under curve. Steady-state distribution volume was calculated as $V_c (1 + k_{12}/k_{21})$, where V_c is the volume of the central compartment and k_{12} and k_{21} are the unidirectional elimination rate constants of alfentanil between central and peripheral compartments.

Potential age-dependent and dose-dependent changes in pharmacokinetic parameters were compared between groups by Student's *t* test for unpaired results. Comparison of parameters among more than two groups (group I, II, and III) was performed by one-way analysis of variance with the Duncan multiple range test. Correlations between age and pharmacokinetic values were studied by least square regression analysis. For correlation of V_{dss} , $t_{1/2}$ beta, and clearance with age, both linear and non-linear equations were tested.

TABLE 1. Patient Characteristics

Group	Patient Number	Sex	Age (Yr)	Weight (kg)	Pathology/Surgery
1 50 μ g/kg <1 Yr	1	M	.9	10.9	Lymphangioma
	2	M	.2	5.2	Cranioectomy
	3	F	.3	4.8	Cleft Lip
	4	F	.9	9.2	Cleft Palate
	5	M	.3	6.8	Cleft lip
2 50 μ g/kg >1 Yr	6	F	4.6	17.7	Otoplasty
	7	M	1.0	8.5	Hypospadias
	8	M	1.6	11.2	Ureteric Reimplant
	9	F	4.7	21.3	Ptosis
	10	F	3.7	14.5	Strabismus
	11	M	4.0	15.0	Strabismus
	12	M	8.5	30.0	Strabismus
	13	M	14.7	43.0	Osteotomy
3 120 μ g/kg >1 Yr	14	M	1.3	11.2	Cleft Palate
	15	M	1.5	12.4	Clubbed Feet
	16	F	1.1	8.1	Colostomy
	17	M	14.0	51.0	Epiphyseal Fixation
	18	M	12.0	36.6	Laminectomy

Results

After the administration of alfentanil, adverse cardiovascular effects as a result of the drug administration (more than 20% change in blood pressure or in heart rate) were not seen with either of the dose regimens. The mean decrease in heart rate was 8.4 (SE 2.3) beats per minute, and the mean decrease in systolic blood pressure was 13.3 (SE 2.8) mmHg. Following incision, heart rate increased 7.4 (SE 1.4) beats per minute and systolic blood pressure increased 14 mmHg (SE 4.1). No correlation could be found between percent change in systolic blood pressure and alfentanil concentration at the time of incision. However, the two children with the lowest plasma concentrations (80 and 94 ng \cdot ml⁻¹) experienced the largest increase in blood pressure with incision (64% and 42%, respectively).

The pharmacokinetic data of the 18 patients are presented in table 2. Figure 1 shows the typical biexponential decline in alfentanil plasma concentrations in a patient receiving 50 μ g \cdot kg⁻¹. No significant difference in $t_{1/2}$ alpha between infants (group I) and children (group II) was found. Similarly, the two groups had similar elimination half-life ($t_{1/2}$ beta), volume of central compartment (V_c), volume of distribution at steady state (V_{dss}), and clearance rate (TBC). No correlation existed between V_{dss} or $t_{1/2}$ beta and ages. There was a weak negative correlation between age and clearance ($r = 0.5$, $P < 0.05$) (fig. 2). The increase in dose from 50 μ g \cdot kg⁻¹ to 120 μ g \cdot kg⁻¹ (group III) resulted in a proportional increase in AUC (from 6784 [SE 583] ng \cdot min \cdot ml⁻¹ to 15982 [SE 1760] ng \cdot min \cdot ml⁻¹).

TABLE 2. Pharmacokinetics after Bolus Injection of Alfentanil (All Values are Mean \pm SE)

Patient Number	Alpha (l·min ⁻¹)	t _{1/2} alpha (min ⁻¹)	Beta (l·min ⁻¹)	t _{1/2} beta (min ⁻¹)	k ₁₂ (l·min ⁻¹)	k ₂₁ (l·min ⁻¹)	k ₁₀ (l·min ⁻¹)	k ₀₁ (l·min ⁻¹)	V _c (l·kg ⁻¹)	V _{dis} (l·kg ⁻¹)	AUC (ng·min·ml ⁻¹)	TBC (ml·min·kg ⁻¹)	Patient Number
50 μ g·kg ⁻¹ <1 yr													50 μ g·kg ⁻¹ <1 yr
1	0.061	11.500	0.008	86.000	0.011	0.048	0.048	0.011	0.188	0.376	5543	9.020	1
2	0.045	15.400	0.009	77.000	0.016	0.027	0.027	0.016	0.404	0.941	4609	10.840	2
3	0.056	12.400	0.007	99.000	0.016	0.032	0.032	0.016	0.267	0.460	5753	8.690	3
4	0.079	8.800	0.014	50.000	0.032	0.035	0.035	0.032	0.174	0.390	8085	6.180	4
5	0.046	15.100	0.010	69.000	0.013	0.037	0.037	0.013	0.198	0.594	6923	7.220	5
Mean	0.057	12.640	0.010	76.200	0.018	0.036	0.036	0.018	0.246	0.552	6183	8.390	Mean
Standard error	0.006	1.220	0.001	8.230	0.004	0.003	0.003	0.004	0.043	0.105	602	0.798	Standard error
50 μ g·kg ⁻¹ >1 yr													50 μ g·kg ⁻¹ >1 yr
6	0.045	15.400	0.008	86.000	0.012	0.032	0.032	0.012	0.232	0.543	6736	7.420	6
7	0.128	5.400	0.016	43.000	0.035	0.058	0.058	0.035	0.142	0.241	6089	8.210	7
8	0.058	12.000	0.006	116.000	0.009	0.040	0.040	0.009	0.219	0.350	5702	8.770	8
9	0.076	9.000	0.015	50.000	0.028	0.040	0.040	0.028	0.179	0.393	6972	7.170	9
10	0.040	17.800	0.005	139.000	0.006	0.031	0.031	0.006	0.171	0.319	9343	5.350	10
11	0.050	13.900	0.010	72.000	0.012	0.042	0.042	0.012	0.246	0.556	4837	10.330	11
12	0.056	12.300	0.015	50.000	0.028	0.035	0.035	0.028	0.262	0.515	5492	9.100	12
13	0.053	13.100	0.006	116.000	0.012	0.028	0.028	0.012	0.195	0.308	9100	5.490	13
Mean	0.053	12.363	0.010	84.000	0.018	0.038	0.038	0.018	0.206	0.416	6784	7.730	Mean
Standard error	0.010	1.347	0.002	12.827	0.004	0.003	0.003	0.004	0.014	0.050	583	0.613	Standard error
120 μ g·kg ⁻¹													120 μ g·kg ⁻¹
14	0.052	13.300	0.010	72.000	0.014	0.037	0.037	0.014	0.220	0.480	14704	8.160	14
15	0.045	15.400	0.013	52.000	0.019	0.032	0.032	0.019	0.338	1.140	11003	10.900	15
16	0.100	6.900	0.015	46.000	0.040	0.040	0.040	0.040	0.173	0.355	17707	6.780	16
17	0.057	12.000	0.012	63.000	0.018	0.037	0.037	0.018	0.202	0.478	14909	7.420	17
18	0.037	19.000	0.008	87.000	0.010	0.030	0.030	0.010	0.188	0.564	21587	5.560	18
Mean	0.058	13.320	0.012	64.000	0.020	0.035	0.035	0.020	0.224	0.603	15982	7.764	Mean
Standard error	0.011	1.994	0.001	7.287	0.005	0.002	0.002	0.005	0.029	0.138	1760	0.893	Standard error

Consequently, clearance rate and volume of distribution at steady state were not affected by the size of the dose.

None of the patients required postoperative ventilation.

Discussion

In order to design a drug-administration scheme for alfentanil in children, it is desirable to determine the population pharmacokinetics for the group. We have, therefore, attempted, in this initial study, to determine whether there is an age-related correlation for pharmacokinetics of alfentanil in children over a broad age range.

In a recent review of the population pharmacokinetics of alfentanil in adults,⁶ both the variability of alfentanil pharmacokinetics between different studies, and inter-individual variability between patients have been quantified using pooled data from four studies. Using a non-linear regression analysis, the effect of six concomitant variables on the plasma concentration

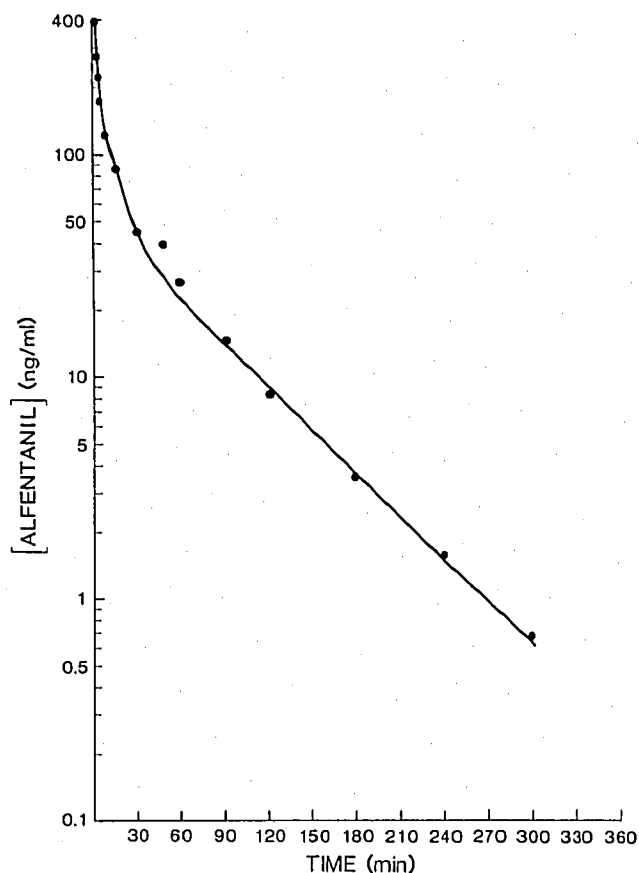


FIG. 1. A typical biexponential decline on one patient receiving alfentanil $50 \mu\text{g} \cdot \text{kg}^{-1}$ as a single 30-s infusion.

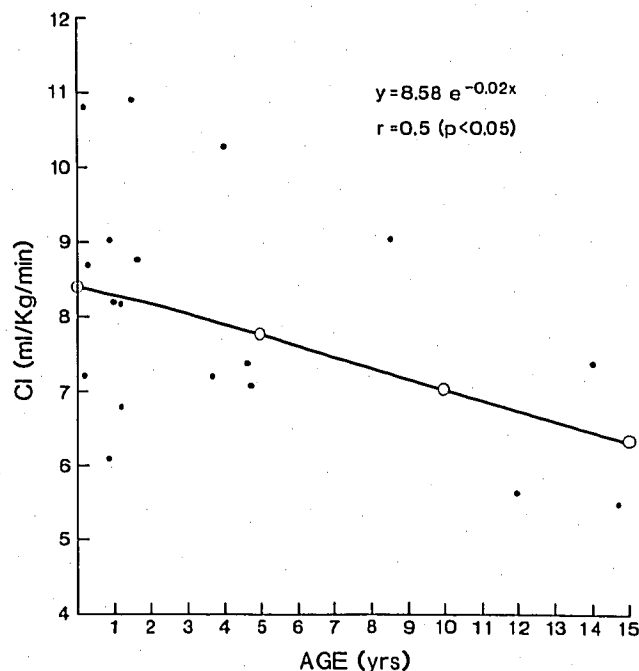


FIG. 2. Correlation between clearance of alfentanil and age in 18 children, aged 3 months to 14 yr.

versus time profile of alfentanil were evaluated. It is appropriate to review this study in light of the pharmacokinetic measurements we have made in children.

We have used a two-compartment model for pharmacokinetic analysis. Although a comparison of models for pharmacokinetics in adults demonstrates that a three-compartment model may best describe alfentanil pharmacokinetics, both two- and three-compartment models have been used.⁷⁻¹¹ Fitting of our data to a three-compartment model did not statistically improve the results. Without statistical demonstration of improvement of our model, we felt it was useful to retain a two-compartment model for comparison with the only other study done of alfentanil kinetics in children.

There is considerable variation in clearance and volume of the central compartment in adults.⁶ The coefficient of variation for unexplained inter-individual variability of clearance is 48%, and of V_c (Volume of Central Compartment) is 33%. It would appear that this variability is no less in children.

A recent study by Meistelman *et al.*¹² was done in children aged 5-8 yr, in which there was a wide inter-individual variation of clearance rates. Although all children in that study were between 4.5 and 7.7 yr and all were healthy, there was a three-fold variability in calculated clearance rates (between 2.7 and $8.3 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$), and a five-fold variability in calculated V_{dss} (range 78 - $369 \text{ ml} \cdot \text{kg}^{-1}$). Although variability in

TABLE 3. A Comparison of Pharmacokinetic Values of Alfentanil Between Adults¹⁰ and Children (Present Study). The Two Studies are Compared Because of the Similar Anesthetic Technique Used and the Employment of Two Comparable Bolus Doses. Values are Mean \pm SE

	Children <1 Yr 50 $\mu\text{g} \cdot \text{kg}^{-1}$	Children 1-14 Yr 50 $\mu\text{g} \cdot \text{kg}^{-1}$	Adults ¹⁰ 50 $\mu\text{g} \cdot \text{kg}^{-1}$
$t_{1/2}$ alpha (min)	12.64 (1.22)	12.36 (1.35)	9.4 (2.65)
$t_{1/2}$ beta (min)	76.20 (8.23)	84.00 (12.83)	93.7 (8.29)
Vdss ($\text{l} \cdot \text{kg}^{-1}$)	0.55 (0.10)	0.42 (0.05)	0.996 (0.32)
TBC ($\text{ml} \cdot \text{min} \cdot \text{kg}^{-1}$)	8.39 (0.80)	7.73 (0.61)	7.58 (2.39)
		Children 1-14 yr 120 $\mu\text{g} \cdot \text{kg}^{-1}$	Adults ¹⁰ 125 $\mu\text{g} \cdot \text{kg}^{-1}$
$t_{1/2}$ alpha (min)		13.32 (1.99)	14.4 (0.82)
$t_{1/2}$ beta (min)		64.00 (7.29)	93.8 (9.31)
Vdss ($\text{l} \cdot \text{kg}^{-1}$)		0.60 (0.14)	0.708 (0.19)
TBC ($\text{ml} \cdot \text{min} \cdot \text{kg}^{-1}$)		7.76 (0.89)	5.06 (1.07)

calculated clearance rates for our study was only two-fold and variation in calculated Vdss was also two-fold, these numbers, nevertheless, still demonstrate wide variability for the population. We originally speculated that the presence of volatile anesthetic agents would affect variability and results (table 3). In light of the suggestion of Maitre *et al.*,⁶ however, that inhalational anesthetics and the duration of anesthesia clearly lacked a significant influence on alfentanil pharmacokinetics, we are unable to explain either the differences in variability of calculated clearance rates and Vdss, or the differences in mean values when we compare the two studies. It would appear that, regardless of the population, variability of clearance, Vc, and Vdss are considerable.

In comparing alfentanil pharmacokinetics in children and adults, Meistelman *et al.*¹² studied eight children and five adults. That study demonstrated a smaller volume of distribution of alfentanil in children ($\text{Vdss } .163 \pm .110 \text{ l} \cdot \text{kg}^{-1}$) as compared with adults ($\text{Vdss } .457 \pm .160 \text{ l} \cdot \text{kg}^{-1}$). Contrary to their results, we have not demonstrated a correlation between age and $t_{1/2}$ alpha, $t_{1/2}$ beta, Vc, or Vdss. The mean values which we have measured are all within the range of values measured in previous adult studies.

Our results for clearance (TBC) are also contrary to the results of Meistelman *et al.*¹² Our studies detected a weak, but significant, negative correlation ($r = .051$, $P < 0.05$) between alfentanil clearance and age. In adults, Maitre *et al.* (retaining a three-compartment model) found that there was a significant association with age and clearance in a linearly decreasing function of age for patients more than 40 yr old. The clearance for phenytoin and theophylline also have a negative correlation with clearance and age in children,¹³ resulting in higher doses per body weight required when compared with adults. (As most drugs, including opiates, demonstrate decreased clearance rates in neonates, and espe-

cially pre-term infants,¹⁴ any extrapolation from results in the older children in our study to a younger age group may be inaccurate.) Because of the previously described relationships between clearance and age, and their consistency with our results, variations in clearance with age should remain a consideration in dosing for alfentanil in children.

Our data indicate that there is no evidence for saturation of alfentanil metabolism in children when a large dose ($120 \mu\text{g} \cdot \text{kg}^{-1}$) is administered; AUC (area under the curve) is proportional to the dose, indicating a similar clearance rate regardless of the size of the dose.

We have been unable to confirm the results of Meistelman *et al.*,¹² which suggested that children have small volume of distribution of alfentanil but a similar clearance of the drug. Based on our data and a recent study on the population pharmacokinetics of alfentanil,⁶ we have been unable to confirm that there is a difference in Vdss between our patients and adults, and we have been unable to demonstrate a relationship between age and Vdss. Although there is a weak negative correlation between alfentanil clearance and age in the children in our study, it is unlikely to be a major consideration for dosing of alfentanil.

Our results suggest that, when a continuous infusion of alfentanil is given to sustain its anesthetic effect, the alfentanil dose rate in pediatric patients may not be different from that required in adults to achieve comparable plasma concentrations, as the clearance rate of the drug is comparable between the two groups. More studies in large numbers are needed in order to verify the putative correlation between age and clearance rate in the pediatric age group.

More studies are also needed to analyze the anesthetic effects of alfentanil in children, primarily in relation to pharmacodynamics. The presence of pancuronium and halothane in our patients may have blunted putative bradycardia and hypotension induced by the

opioid. In addition, further studies are required in children less than 3 months of age to determine the guidelines for the use of alfentanil in the very young.

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