

A Comparison of Alfentanil Pharmacokinetics in Children and Adults

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The pharmacokinetics of alfentanil have been studied in eight children aged between 4 and 8 yr and five adults during general anesthesia. All patients were given 20 µg/kg alfentanil as an intravenous bolus injection. Plasma concentrations were measured at intervals up to 6 h by radioimmunoassay. Plasma protein binding was measured by equilibrium dialysis using tritiated alfentanil. The optimal pharmacokinetic model for alfentanil was an open two-compartment model. Total apparent volume of distribution ($V_{d\alpha}$) was 457 ± 160 ml/kg in adults and 163 ± 110 ml/kg in children ($P < 0.01$). When recalculated by surface area $V_{d\alpha}$ was still decreased in children ($P < 0.01$). Plasma clearance (Cl) was similar in the two groups. Terminal elimination half-life was significantly shorter in children (40 ± 9 min) than in adults (97 ± 22 min; $P < 0.01$). The shorter elimination half-life could be due to the smaller total apparent volume of distribution in children. Plasma protein binding was comparable between children and adults and could not explain the smaller volume of distribution in children. It is suggested that the smaller volume of distribution of alfentanil in children is a result of the decreased percentage of fat tissue in children. (Key words: Anesthesia; pediatrics. Anesthetics, intravenous: alfentanil. Pharmacokinetics: alfentanil, children, adults.)

ALFENTANIL HYDROCHLORIDE, a chemical derivative of fentanyl, is a new opioid with a wide margin of safety and a potency in humans approximately one-seventh that of fentanyl.¹ Pharmacokinetic studies in adults have shown that alfentanil has a short elimination half-life (95 min) and a small volume of distribution.^{2,3} The aim of our present study was to compare the pharmacokinetic properties of a single intravenous dose of alfentanil in children and adults.

Patients and Methods

Eight children aged between 4 and 8 yr (5.4 ± 1.1 yr, mean \pm SD) undergoing minor genitourinary surgery and five adults between the ages of 25 and 40 yr (31.3 ± 3.8 yr) were studied. Patient data are shown in table 1. The protocol was approved by the local ethical committee, and informed consent was obtained from the parents of the children and from the five adults studied. All the pa-

tients were ASA P. S. I, and none received preanesthetic sedation. In children anesthesia was induced by mask using enflurane at an inspired mean concentration of 2% and nitrous oxide (50%) in oxygen (50%). Once the child was unconscious, an indwelling catheter was introduced into a vein of the forearm. Alcuronium (200 µg/kg) was used to facilitate orotracheal intubation. In adults anesthesia was induced with thiopental 5-7 mg/kg intravenously, then alcuronium (200 µg/kg) was injected and orotracheal intubation performed. In all the patients ventilation was controlled and adjusted by capnography to maintain P_{CO_2} between 30-35 mmHg. Anesthesia was maintained in children and adults with a nitrous oxide (50%)-oxygen (50%) mixture and enflurane at a 2% inspired concentration. The same calibrated vaporizer was used during the study.

Alfentanil (20 µg/kg) was injected as a bolus through a small needle into a vein of the opposite arm 10-15 min after induction of anesthesia. Venous blood samples (2 ml) were drawn from the indwelling catheter a few min before administration, 1, 3, 5, 7, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, and 360 min after injection of alfentanil. Plasma was separated from blood samples by centrifugation and stored at -20° C until assay. Alfentanil concentrations were determined in duplicate by radioimmunoassay using rabbit antialfentanil antibody. This radioimmunoassay had a sensitivity of 0.1 ng/ml and a coefficient of variation of 3.7% over a range of 0.18-4.4 ng/ml. There was no cross-reaction between alfentanil and its metabolites.⁴

Plasma alfentanil concentration time-data from each patient were fitted to a biexponential equation interpreted as a two-compartment open pharmacokinetic model using nonlinear least-squares regression analysis with Marquardt algorithm. Weighting was achieved by the inverse square of the predicted plasma levels. § Half-lives ($T_{1/2\alpha}$ and $T_{1/2\beta}$), volume of the central compartment (V_c), volume of distribution at steady state (V_{dss}), apparent volume of distribution ($V_{d\beta}$), plasma clearance (Cl), first order rate constants (k_{12} , k_{21}) and elimination rate constant (k_e) were calculated using equations described by Gibaldi and Perrier.⁵

Plasma protein binding was measured by equilibrium dialysis between plasma (1 ml) and buffer containing tri-

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§ SAS User's Guide. Cary NC, 1979, SAS Institute, pp 317-329.

TABLE 1. Age and Weight of Patients

Subject	Age (yr)	Body Weight (kg)	Surgical Procedure
Children			
1	4.7	20	Orchiopexy
2	5.5	22	Inguinal hernia
3	7.7	23	Orchiopexy
4	4.5	14	Orchiopexy
5	4.8	24	Skin graft
6	4.5	20	Orchiopexy
7	6.2	23	Inguinal hernia
8	4.9	22	Orchiopexy
Mean \pm SD	5.4 \pm 1.1	21 \pm 3	
Adults			
1	28	66	Inguinal hernia
2	35	55	Skin graft
3	32	58	Endoscopy
4	34	60	Endoscopy
5	27	60	Inguinal hernia
Mean \pm SD	31 \pm 4	58 \pm 6	

tium-labeled radioactive alfentanil at two concentrations of 50 and 500 ng/ml. Alfentanil was purified by high performance liquid chromatography (HPLC) and the specific activity was 23.1 Ci/mmol. The cells were rotated at 20 rpm in a bath maintained at 37° C during 4 h. Initial pH of the buffer and eventually of the plasma were adjusted to give a final pH of 7.4. Drug concentrations were determined by radioactivity measurements. Quench correction was made by the external standards ratio method. After equilibrium had been reached, drug concentration in the buffer was equal to concentration of free drug (concentration unbound), whereas concentration of alfentanil in the protein compartment was equal to the sum of the concentration of both free and bound

drug (concentration bound). Free fraction was calculated as the concentration of drug in the buffer divided by the concentration in plasma.⁶ A two-tailed Mann-Whitney U-test was used to evaluate the differences between the two groups, a value of $P < 0.05$ was considered to be significant. All the results are expressed as mean \pm SD.

Results

Individual pharmacokinetic data are shown in tables 2 and 3 and the plasma alfentanil concentrations as a function of time are shown in figure 1. The rapid initial disappearance corresponded to a distribution phase of 5.1 \pm 2.1 min in children as compared with that of 10.4 \pm 7.3 min in adults ($P < 0.05$). The volume of the central compartment was statistically ($P < 0.01$) smaller in children (70 \pm 56 ml/kg) than in adults (187 \pm 36 ml/kg). The total plasma clearance did not differ significantly in the two groups. The total apparent volume of distribution at steady state was also significantly smaller ($P < 0.01$) in children (163 \pm 110 ml/kg) than in adults (457 \pm 160 ml/kg), leading to a shorter elimination half-life in children (40 \pm 9 min) than in adults (97 \pm 22 min) ($P < 0.01$). Plasma clearance recalculated by surface area did not differ significantly between children and adults, whereas the difference was still significant ($P < 0.01$) for $V_{d_{ss}}$ recalculated by surface area. No fluctuations in plasma levels were observed.

In children plasma protein binding of alfentanil was 94.4 \pm 1.5% at an alfentanil concentration of 50 ng/ml and 92.4 \pm 2.4% at 500 ng/ml. In adults plasma protein binding was 92.3 \pm 1.3% and 91.8 \pm 1.5% for the 50 and 500 ng/ml concentrations of alfentanil, respectively. At the two concentrations studied plasma protein binding

TABLE 2. Individual Pharmacokinetic Data

Subject	V_1 (ml \cdot kg ⁻¹)	$V_{d_{ss}}$ (ml \cdot kg ⁻¹)	$V_{d_{ss}}$ (ml \cdot kg ⁻¹)	$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (min)	Cl (ml \cdot min ⁻¹ \cdot kg ⁻¹)
Children						
1	47	108	169	4.6	34	3.4
2	127	306	423	5.9	50	5.9
3	184	369	684	9.6	57	8.3
4	59	113	225	6.0	34	4.6
5	34	96	202	4.1	38	3.7
6	38	94	208	3.7	30	4.8
7	49	144	259	4.3	41	4.4
8	20	78	148	2.7	38	2.7
Mean \pm SD	70 \pm 56	163 \pm 110	290 \pm 180	5.1 \pm 2.1	40 \pm 9	4.7 \pm 0.6
Adults						
1	247	738	863	4.8	83	7.2
2	175	412	505	8.6	89	3.9
3	184	362	532	22.8	134	2.7
4	183	428	548	10.5	96	3.9
5	149	348	387	5.21	81	3.3
Mean \pm SD	187 \pm 36†	457 \pm 160†	567 \pm 177†	10.4 \pm 7.3*	97 \pm 22†	4.2 \pm 1.7

Mean values significantly different between children and adults; * $P < 0.05$. † $P < 0.01$.

was not significantly different between the children and adults.

Discussion

In adults alfentanil pharmacokinetics can be described by a biexponential equation corresponding to an open two-compartment model.^{7,8} In our study the addition of a third term was possible in adults but did not improve the model as in the studies of Schüttler and Stoeckel⁷ or Bower and Hull.⁸ In children the decreased distribution phase makes it impossible to use a tricompartamental model. The smaller distribution half-life in children could be due to the enhanced penetration into highly perfused tissues. The smaller volume of the central compartment results in higher initial plasma concentration in children.

The most important difference between children and adults is that the total apparent volume of distribution at steady state is 2.8 times larger in adults than in children. This difference could be due to the lower percentage of fat tissue in children, which increases from 13 to 16% in children between 5 and 8 yr to 20–25% in adults.⁹ Alfentanil is bound extensively to plasma proteins and to a larger extent to α -1 acid-glycoprotein than to albumin. In this study protein binding was comparable to the results of Meuldermans *et al.*⁶ and Ferrier *et al.*¹⁰ in normal patients, and there were no significant differences between children and adults. Thus, the decrease in $V_{d_{ss}}$ cannot be explained by changes in protein binding.

Hepatic function in children approaches adult levels at approximately 2–3 yr of age and could, in part, explain that plasma clearance does not differ significantly between children and adults.¹¹ The alfentanil hepatic extraction coefficient can be estimated by dividing plasma clearance by the hepatic plasma flow because alfentanil is mainly present in plasma and weakly transported by red blood cells.⁸ The alfentanil extraction coefficient is between 0.3^{8,10} and 0.6² in adults, and a value of 0.54 was obtained in children in our study. Differences between children and adults are probably not explained by changes in regional blood flow such as changes in hepatic blood flow. No patients in the two groups underwent abdominal surgery that involved a profound decrease in hepatic blood flow.¹²

The influence of inhalational agents on alfentanil pharmacokinetics is of particular interest because these agents could alter drug distribution and uptake or hepatic blood flow. There are few data about the effects of enflurane on drug distribution, but it has been shown that enflurane did not affect the distribution of drugs such as thiopentone in humans.¹³ Enflurane involves a decrease in hepatic blood flow, but hepatic vascular resistances decrease to preserve portal blood flow.¹⁴ Furthermore, the surgical procedures lasted less than 1 h in our study; therefore, alfentanil distribution occurred during enflur-

TABLE 3. Individual Transfer Rate Constants

Subject	k_{12} (min^{-1})	k_{21} (min^{-1})	k_e (min^{-1})
Children			
1	0.055	0.041	0.074
2	0.050	0.035	0.046
3	0.020	0.019	0.045
4	0.028	0.030	0.078
5	0.051	0.029	0.107
6	0.049	0.034	0.125
7	0.059	0.031	0.088
8	0.100	0.034	0.137
Mean \pm SD	0.051 \pm 0.024	0.032 \pm 0.006	0.088 \pm 0.034
Adults			
1	0.082	0.041	0.029
2	0.038	0.027	0.023
3	0.010	0.010	0.015
4	0.030	0.022	0.022
5	0.068	0.051	0.035
Mean \pm SD	0.045 \pm 0.029	0.030 \pm 0.16	0.025 \pm 0.008*

Mean values significantly different between children and adults; * $P < 0.01$.

ane anesthesia, whereas most of the elimination phase occurred during the postoperative period. However the conditions of the study were similar between children and

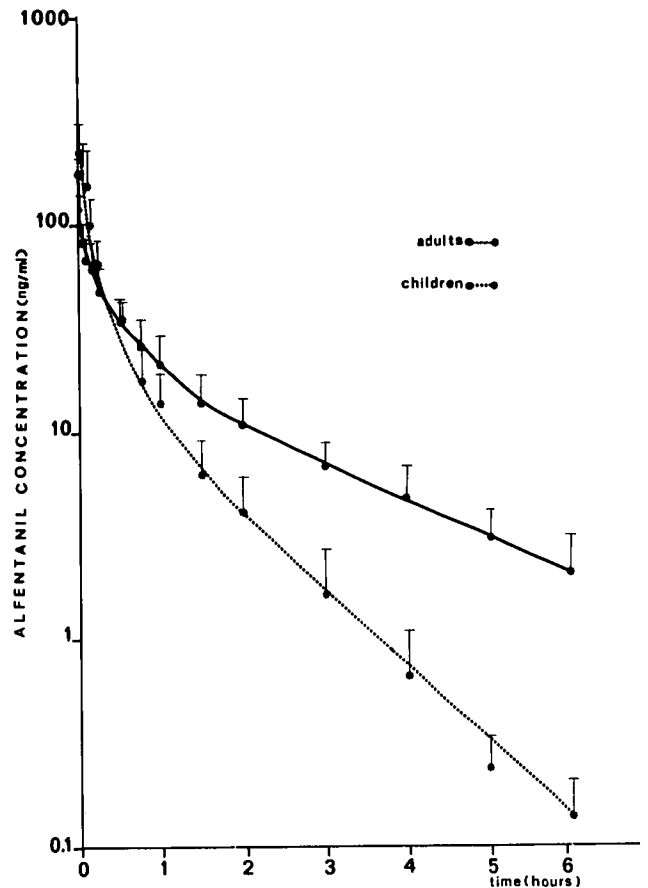


FIG. 1. Alfentanil plasma decay curves for children (*) and adults (●) following a single intravenous bolus (20 $\mu\text{g}/\text{kg}$). Mean \pm SD.

adults, and the elimination half-life of alfentanil in adults was close to the values observed by Bovill *et al.*² or Ferrier *et al.*¹⁰ in adults during anesthesia without enflurane.

Our results have implications for pediatric anesthesia. The duration of narcotic effects of alfentanil, after a large single bolus or a continuous infusion, is determined by the elimination half-life.¹⁵ Thus, recovery time will be more rapid in children than in adults because of the shorter elimination half-life. The smaller $V_{d_{ss}}$, in children between 4 and 8 yr, is of clinical significance in that the risk of accumulation will be less than it might be in adults, particularly after repeated boluses or continuous infusion. The steady-state concentration resulting from a continuous infusion of alfentanil is equal to the infusion rate divided by the plasma clearance. Therefore, the infusion rate required to maintain a comparable steady-state plasma concentration does not change with age because the plasma clearance does not differ significantly between children and adults. On the other hand, termination of the narcotic effects at the end of the infusion will be more rapid in children than in adults because of the shorter elimination half-life in children.

Children aged between 4 and 8 yr were studied; therefore, these data may not apply to infants. Further pharmacokinetic studies are required to determine the disposition of alfentanil in neonates and infants.

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