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The Pharmacokinetics of Alfentanil (R39209): A New Opioid Analgesic

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The pharmacokinetics of alfentanil (R39209), a new short-acting opioid analgesic, have been studied in eleven patients. Six patients were given 50 μg/kg alfentanil and five patients 125 μg/kg as an intravenous bolus injection. Plasma concentrations were measured at intervals up to 6 h (50 μg/kg) or 8–10 h (125 μg/kg), using a specific radioimmunoassay technique. Plasma concentrations declined triexponentially in both groups. The initial elimination of alfentanil from the plasma was very rapid with 90% of the administered dose leaving the plasma within 30 min. The average half-lives for the three phases were similar for both groups. The combined mean (±SEM) half-lives for the 11 patients for the rapid and slow distribution phases were short ($t_{1/2}\pi$ = 1.2 ± 0.26 min, $t_{1/2}\alpha$ = 11.6 ± 1.63 min). The elimination half-life, $t_{1/2}\beta$ was 94 ± 5.87 min which is considerably shorter than that of other opioids. The mean (±SEM) total body clearance was 6.4 ± 1.39 ml · kg^{-1} · min^{-1} and the volume of distribution (Vd) was 0.86 ± 0.194 l/kg. The latter is considerably less than reported values for the chemically related drug, fentanyl, and suggests that alfentanil may have a lower tissue binding affinity than fentanyl. The rapid elimination and short duration of clinical action suggests the feasibility of repeated administration of alfentanil and its use by continuous intravenous infusion. (Key words: Analgesics: alfentanil. Anesthetics, intravenous: alfentanil. Pharmacokinetics: alfentanil.)

ALFENTANIL HYDROCHLORIDE is a new opioid analgesic currently undergoing investigation in Europe.[1–5] It is chemically related to fentanyl (fig. 1). In the tail withdrawal test in rats, alfentanil is approximately one-quarter as potent as fentanyl and has one-third the duration of action, with a safety ratio (LD_{50}/ED_{50}) of 1080.¶ Hemodynamic studies in ventilated dogs have shown the acute toxicity of alfentanil to lie between that of morphine and fentanyl, with cardiovascular stability maintained with doses up to 5 mg/kg.[1] Studies in humans have shown alfentanil to be effective as an analgesic supplement to oxygen–nitrous oxide anesthesia for gynecologic surgery[6] and as a total opioid anesthetic for cardiac surgery.[7] A study comparing alfentanil and fentanyl as analgesics for postoperative pain suggested that alfentanil was approximately one-third as potent as fentanyl in humans with one-third the duration of action.[8] To date, there have been no reports on the pharmacokinetic properties of alfentanil in humans, although one study in dogs described triexponential elimination of the drug from plasma with elimination half-lives between 135 and 168 min.[9]

A radioimmunoassay recently has been developed which enables plasma concentrations of alfentanil to be measured as low as 0.1 ng/ml.[10] We have used this method to study the pharmacokinetics of the drug, given as a single injection in humans.

Methods

Eleven patients undergoing a variety of surgical procedures were studied. Informed consent was obtained from each patient. Details of the patients and of the operative procedures are given in table 1.

Six patients were given 50 μg/kg alfentanil and five patients 125 μg/kg. Premedication was either 3–5 mg lorazepam or 10 mg diazepam orally 1.5 h before surgery. Anesthesia was induced with a sleep dose of thiopental (4.0 to 5.2 mg/kg) followed by 50–75 mg suxamethonium and the patient's trachea was intubated. The lungs were ventilated with oxygen–nitrous oxide ($F_{I_{O_2}}$ = 0.3) and anesthesia was supplemented with either halothane 0.5% or ethrane 1% inspired concentration as required. Pancuronium, 0.1 mg/kg, was used for muscle relaxation. A 14-gauge cannula was inserted into the superior vena cava via the external jugular vein for the withdrawal of blood samples. During surgery, a maintenenace infusion of Ringer's solution was given at 7–10 ml · kg^{-1} · h^{-1}. Blood loss in excess of 300 ml was replaced with packed red blood cells and fresh frozen plasma. Ventilation was adjusted to maintain an end-tidal CO_2 concentration between 4.5–5.0%. In one patient undergoing craniotomy (patient 10), moderate hyperventilation (end-tidal CO_2 concentration 3.7–4.0%) was used for a 45-min period during surgery, between 1.25–2 h after the administration of alfentanil. One-lung anesthesia was used in one patient (patient 8) for

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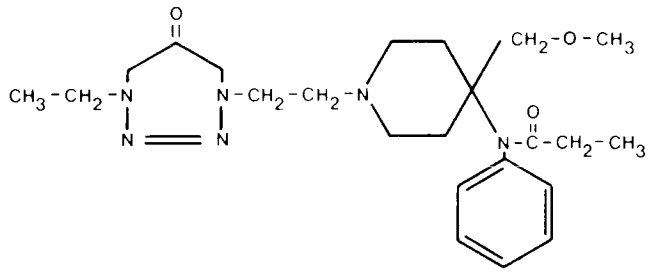
Alfentanil



Fentanyl

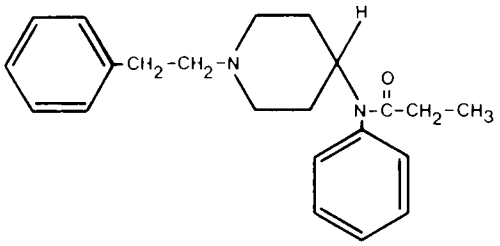


FIG. 1. Chemical structure of alfentanil (R39209) and fentanyl.

30 min between 1 and 1.5 h after alfentanil administration.

After intubation a control blood sample was obtained and the appropriate dose of alfentanil was injected intravenously as a bolus into an arm vein. Blood samples were taken 1, 2, 3, 5, 10, 15, 30, 45, and 60 min and thereafter every hour until 6 h (50 μg/kg group) or 8–10 h (125 μg/kg group) after injection. Plasma was separated from blood samples and stored at −26° C until assayed. Alfentanil concentrations were determined in duplicate by radioimmunoassay. The procedure is similar to that employed for fentanyl,[11] but using antiserum to alfentanil obtained from rabbits after repeated injections with an alfentanil hapten chemically linked to bovine serum albumin. There was no significant cross-reactivity between alfentanil and any of its likely metabolites, and fentanyl showed cross-reactivity at a molar ratio greater than 1000. The average intra- and inter-assay coefficients of variation were 3.7% and 3.3%, respectively, over a range of 0.18 to 4.4 ng/ml. Plasma samples from two patients were assayed separately using a liquid-liquid extraction procedure which is specific for the unchanged drug. The equation of the regression line calculated for the plasma concentrations of alfentanil determined after extraction *vs.* concentrations measured directly was $y = 0.997 + 1.27x$. A detailed description of the assay procedure is being published separately.[10]

The plasma alfentanil concentration-time data from each patient was fitted by computer to bi- and tri-exponential equations using weighted nonlinear least-square regression analysis. Weights of $1,1/Ct, 1/Ct^2$ were used, (where Ct = alfentanil concentration at time t) and the optimal choice in each case determined by the methods described by Wagner.[12] The choice of a two- or three-compartment model was determined by F-ratio testing.[13] Volumes of distribution, total body clearance, and the apparent first-order intercompartmental transfer rate constants were calculated using equations described by Gibaldi and Perrier.[14] Results are expressed as means ± SEM. Comparison between groups was by unpaired Student's *t* test, and *P* values < 0.05 were considered significant.

TABLE 1. Patient Details

Patient Number	Sex	Age (yr)	Weight (kg)	ASA Class	Operation
50 μg/kg					
1	Male	50	78	II	Mediastinoscopy
2	Male	34	79	II	Craniotomy
3	Female	40	67	I	Laminectomy
4	Female	22	75	I	Strabismus correction
5	Male	64	70	I	Laminectomy
6	Female	43	70	I	Laminectomy
Mean		42	73		
± SEM		5.8	2.0		
125 μg/kg					
7	Male	63	80	II	Pneumonectomy
8	Male	63	69	II	Lobectomy
9	Female	19	52	I	Laminectomy
10	Female	55	64	II	Craniotomy
11	Male	23	80	I	Laminectomy
Mean		45	69		
± SEM		9.8	5.3		

Results

The plasma concentration of alfentanil fell rapidly after injection, 90% of the administered dose having left the plasma within 30 min. The plasma concentration decay curves were best described by triexponential equation in all patients (fig. 2). No transient increases in plasma alfentanil concentrations, such as have been described for fentanyl,[15,16] were observed in any patient.

Detailed kinetic parameters are shown in tables 2 and 3. Neither the half-lives nor the dose/intercept ratios were significantly different between the groups. The result from all 11 patients therefore have been combined and will be referred to in the remainder of the article. The average half lives for the π, α, and β phases were 1.2 ± 0.26 min, 11.6 ± 1.63 min, and 94 ± 5.9 min, respectively. The calculated apparent volume of the central compartment (Vc) was 0.097 ± 0.0186 l/kg, and the volume of distribution (Vd) was 0.86 ± 0.94 l/kg. Average total body clearance (Cl) was 6.4 ± 1.39 $ml \cdot kg^{-1} \cdot min.^{-1}$ The apparent transfer rate constants between the central compartment and compartment 2 were similar (K_{12} = 23 ± 3.9 h^{-1}, K_{21} = 19 ± 3.5 h^{-1}), whereas the rate constant K_{13} was 4.4 times greater than K_{31}.

The time intervals between administration of alfentanil and termination of surgery ranged from 45–200 min in the low-dose group and from 120–360 min in the high-dose group. No respiratory depression in the postoperative period was observed. One patient in each group developed a 20 mmHg fall in systolic pressure immediately after administration of the drug which returned to normal within 2 min. Hypotension was not observed in the remaining patients.

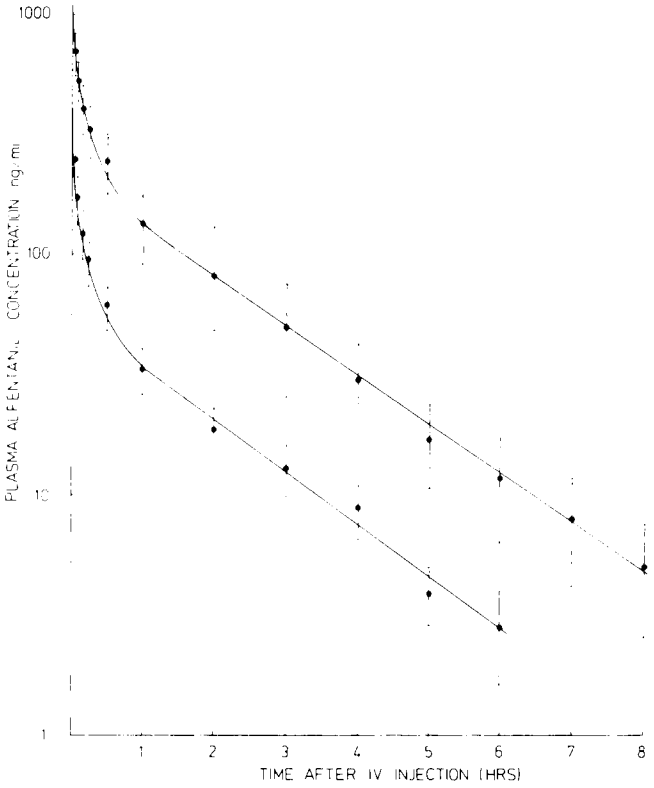


FIG. 2. Plasma concentrations of alfentanil (R39209) after 50 μg/kg (lower curve) and 125 μg/kg (upper curve). Each data point represents the mean ± SEM for each dose.

Discussion

The results of this study demonstrate that the pharmacokinetics of alfentanil can be described by a three-compartment model, with the plasma concentration after bolus intravenous injection declining triexponentially. In this respect alfentanil is similar to fentanyl, to which it is chemically related. The distribution of alfentanil is very rapid, reflected by short half-lives of the rapid and slow distribution phase ($t_{1/2}\pi$ = 1.2 ± 0.26 min, $t_{1/2}\alpha$ = 11.6 ± 1.63 min). These values are similar to those described for fentanyl in humans.[17,18] The terminal elimination half-life ($t_{1/2}\beta$), 94 ± 5.9 min, however, is considerably shorter than the reported values in humans for fentanyl which vary between 219 min[18] and 495 min.[19] This is in keeping with the short duration of action reported by other clinical investigators.[3–5]

There was considerable variation between individual patients in the P, A, and B intercepts, and consequently in the calculated kinetic parameters. Such variation is common in pharmacokinetic studies and may indicate wide individual variations in the apparent volumes of distribution for the drug. Although in this study every effort was made to maintain hydration and to adequately replace blood loss, some changes in plasma and extracellular volume are likely to have occurred during and after surgery. These changes, together with alterations in the plasma protein concentration and the degree of protein binding, can influence drug distribution.[20–22] It is important to emphasize that this study was done for surgical patients whose ages ranged from 22–64 years, who had a variety of operative procedures. These patients could be expected to show more variation than individuals normally chosen for pharmacokinetic studies, *i.e.*, young, healthy adults. However, since alfentanil is likely to be used clinically in patients comparable to those studied here, a knowledge of the expected variation in kinetic parameters is of importance.

Incomplete mixing of the drug in the plasma volume in the period immediately after administration and slight variations in the sampling times also may have been partly responsible for these variations.

TABLE 2. Alfentanil Pharmacokinetics after Bolus Injection

Patient Number	P (ng/ml)	π (min^{-1})	$t_{½}\pi$ (min)	A (ng/ml)	α (min^{-1})	$t_{½}\alpha$ min	B ng/ml	β min^{-1}	$t_{½}\beta$ min	r^{2}*
50 μg/kg										
1	381	0.280	2.47	285	0.059	11.6	59.9	0.0058	118.7	0.9884
2	472	0.223	3.11	115	0.032	21.6	24.2	0.0072	96.3	0.9998
3	494	1.373	0.50	266	0.109	6.4	78.6	0.0063	109.3	0.9998
4	131	1.595	0.43	57	0.152	4.6	17.0	0.0072	97.1	0.9997
5	190	1.103	0.63	62	0.108	6.4	31.9	0.0091	76.5	0.9998
6	1402	0.979	0.71	130	0.124	5.6	98.9	0.0108	64.1	0.9999
Mean	512	0.926	1.31	152	0.097	9.4	51.7	0.0077	93.7	
± SEM	187.9	0.2304	0.477	40.8	0.0179	2.65	13.39	0.00076	8.29	
125 μg/kg										
7	655	0.739	0.94	469	0.051	13.5	481	0.0074	93.3	0.9990
8	1997	0.519	1.34	551	0.046	15.0	182	0.0090	76.9	0.9993
9	996	0.477	1.45	320	0.057	12.1	103	0.0085	81.4	0.9996
10	898	0.876	0.79	314	0.048	14.4	51	0.0054	129.3	0.9982
11	980	0.907	0.76	284	0.040	17.0	88	0.0079	87.9	0.9991
Mean	1105	0.709	1.06	388	0.048	14.4	181	0.0076	93.8	
± SEM	321.1	0.0888	0.142	51.9	0.0027	0.82	78.0	0.00063	9.31	

P, A, B = the ordinal intercepts computed from the least-square analysis of the data; π, α, β = the first-order rate constants; and $t_{½}\pi$, α, β, = the half-lives for the rapid (π) and slow (α) distribution phase and the elimination phase (β).

* $r^{2} = \frac{\Sigma(\text{observed})^{2} - \Sigma(\text{deviation})^{2}}{\Sigma(\text{observed})^{2}}$

Since the intercepts were proportional to dose, and the decay curves for both doses were parallel, kinetics remained first-order and saturation of compartments did occur with the higher dose. The apparent transfer rate constants between the central compartment and peripheral compartment 2 were similar and large. The rapid decline in plasma alfentanil concentrations was therefore due to rapid equilibration between these two compartments. The equivalent transfer rate constants for compartment 3 were considerably lower and K_{13}/K_{31} ratio was much greater than that for K_{12}/K_{21}. Compartment 3 thus acts as a tissue reservoir maintaining plasma concentrations during the elimination phase. This reservoir effect of compartment 3, however, is less pronounced for alfentanil than for fentanyl since the K_{13}/K_{31} ratio for alfentanil is considerably lower than that reported for fentanyl.[18] The apparent volume of distribution (Vd) for alfentanil (0.86 l/kg) is much smaller than that of fentanyl (4 l/kg).[18] Alfentanil has a higher protein binding (92%) than fentanyl (84%) and

TABLE 3. Calculated Kinetic Variables after Bolus Injection of Alfentanil

Patient Number	Vc (l/kg)	Vd (l/kg)	Cl ($ml \cdot min^{-1} \cdot kg^{-1}$)	K_{10} (h^{-1})	K_{12} (h^{-1})	K_{13} (h^{-1})	K_{21} (h^{-1})	K_{31} (h^{-1})
50 μg/kg								
1	0.0689	0.522	3.05	2.65	4.75	2.86	9.66	0.82
2	0.0818	0.766	5.51	4.04	5.32	1.36	4.41	0.62
3	0.0596	0.519	3.29	3.31	38.73	8.57	37.01	1.67
4	0.2442	2.472	17.64	4.33	45.42	14.14	39.17	2.21
5	0.1763	1.293	11.72	3.99	32.91	8.92	25.02	2.33
6	0.0307	0.398	4.30	8.42	23.35	19.39	13.17	2.57
Mean	0.1151	0.996	7.58	4.38	22.75	8.93	20.68	1.69
± SEM	0.03756	0.3236	2.39	0.836	5.951	2.685	5.563	0.332
125 μg/kg								
7	0.0778	0.225	1.67	1.28	16.18	1.68	27.01	1.76
8	0.0458	0.386	3.48	4.56	16.07	2.75	10.07	1.02
9	0.0881	0.743	6.32	4.31	12.95	3.65	10.56	1.10
10	0.0989	1.362	7.31	4.43	30.06	3.59	17.04	0.65
11	0.0924	0.824	6.49	4.227	33.20	2.54	16.45	0.91
Mean	0.0806	0.708	5.06	3.76	21.69	2.84	16.23	1.09
± SEM	0.00935	0.1974	1.065	0.622	4.127	0.365	3.058	0.185

Vc = apparent volume of the central compartment; Vd = apparent volume of distribution; Cl = total body clearance; K_{10} = elimination rate constant; and K_{12} to K_{31} = transfer rate constants between compartments.

has a lower lipid solubility as measured by the heptane/water partition coefficient (λ) at 37° C and *p*H 7.4. For alfentanil, λ was 2.5, and for fentanyl, λ was 9.0 (Woestenborgs: personal communication). Both differences are consistent with the lower volume of distribution of alfentanil. This smaller volume of distribution together with the higher total clearance can explain the shorter elimination half-life of alfentanil.

The shorter elimination rate of alfentanil can explain the considerably shorter clinical duration of action of this drug compared with other opioids and has important implications for the practicing anesthetist. Accumulation after repeated doses will be reduced considerably. Preliminary results of an investigation in progress suggest that a minimum plasma alfentanil concentration of approximately 300 ng/ml is required to maintain adequate surgical anesthesia in patients ventilated with 40% N_2O/O_2. Plasma levels fall below 300 ng/ml after approximately 3–5 min following a dose of 50 μg/ml, and within 15–20 min with a dose of 125 μg/kg. The short duration of action of alfentanil also makes feasible its administration as a continuous infusion to provide the analgesic component of anesthesia or for the achievement of basal analgesia in intensive care patients.

In conclusion, we have demonstrated that the pharmacokinetics of alfentanil can be described by a three-compartment open model. The half-lives of the rapid and slow distribution phases are short and comparable to those for fentanyl. The volume of distribution is smaller than that of fentanyl, resulting in a much shorter elimination half-life. Further pharmacokinetic investigations are required to establish the disposition of this drug after multiple dosing and during continuous intravenous infusion.

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