Aging and alfentanil disposition in healthy volunteers and surgical patients

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We studied the pharmacokinetic disposition of alfentanil in 20 volunteers and in 15 surgical patients 20–72 years old. Pharmacokinetic disposition was first order and was well described by a two-compartment open model. Central-compartment volume of distribution was 0.131 ± 0.087 L · kg^{-1} (mean ± SD) in young healthy volunteers and decreased modestly with increasing age ($r = -0.32$, $P < 0.05$). However, apparent volume of distribution at steady-state, 0.404 ± 0.205 L · kg^{-1} for the whole study cohort, was not age-related. Plasma clearance of alfentanil in young healthy subjects, 9.3 ± 6.3 ml · kg^{-1} · min^{-1}, also showed an inverse relationship with age ($r = -0.54$, $P < 0.001$), and was not affected by surgical stress in subjects older than 60 years. Cigarette smoking and sex of the subjects did not contribute to interindividual differences in the kinetic disposition of this drug. Our finding that interindividual differences in disposition of alfentanil were the least in older subjects suggests that its pharmacological effects related to pharmacokinetic disposition should be most predictable in the elderly.

Key words

AGE FACTORS: pharmacokinetics; ANAESTHESIA: geriatric; ANAESTHETICS, INTRAVENOUS: alfentanil; PHARMACOKINETICS: distribution, kinetics, models.

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Alfentanil is a new potent synthetic opioid related to fentanyl, with a short plasma half-life and relative cardiovascular stability observed during its use in clinical anaesthesia.[1,2] The drug is eliminated from the body primarily by hepatic conversion to inactive metabolites.[2] Low plasma concentrations after its administration have resulted in the widespread use of radioimmunoassay for quantitation of alfentanil.[3–9] The use of gas–liquid chromatography is a feasible and more specific technique for alfentanil quantitation.[11–13] Some studies suggest impaired plasma clearance of alfentanil with increasing age,[7,13] but there is a lack of consistency in this interpretation, even with reports from the same investigators.[14,15] Therefore, we report below the results of our studies with a specific gas chromatographic assay on the kinetic disposition of alfentanil in healthy young and old volunteers and in surgical patients, to determine if data from normal healthy volunteers apply to surgical patients and to reassess previous reports of age-associated changes in its kinetic disposition.

Methods

Alfentanil pharmacokinetics were determined in 10 young and ten old healthy volunteers, and in 15 surgical patients. The age of the young and old healthy volunteers was 26 ± 4 and 65 ± 4 years respectively (mean ± SD). Their weights were 70.2 ± 16.3 and 74.6 ± 10.5 kg respectively and there were equal numbers of males and females in each group. Young females (55.8 ± 5.7 kg) weighed less than all other healthy volunteers. Demographic data for the surgical patients are presented in Table I, and American Society of Anesthesiologists (ASA) physical status classification is indicated for each of the surgical patient volunteers.[16] The protocols were approved by the appropriate institutional human ethics committees and signed informed consent was obtained from all participants.

Healthy volunteers protocol

Young and older subjects whose good health was assured by history, physical and laboratory examinations, and who were not taking any other medication, presented to

TABLE I Demographic characteristics of surgical patients in whom alfentanil pharmacokinetics were determined

Subject	*Age (yr)*	*Sex*	*Weight (kg)*	*Physical Status (ASA)*	*Drug Dose ($\mu g \cdot kg^{-1}$)*	*Surgical procedure*	*Smoking status*
1	23	M	89.1	1	180	Iliac bone graft	Smoker
2	31	M	64.1	1	175	Septorhinoplasty	Smoker
3	37	M	67.0	1	175	Inguinal herniorrhaphy	Smoker
4	37	M	66.4	1	175	Inguinal herniorrhaphy	Smoker
5	45	M	104.5	1	175	Polypectomy	Smoker
6	47	M	75.0	1	175	Ankle debridement	Smoker
7	53	M	82.0	2	175	Pylolithotomy	Smoker
8	55	M	92.7	2	143	Sigmoid colectomy	Nonsmoker
9	56	M	67.0	1	175	Polypectomy	Nonsmoker
10	58	M	89.5	2	151	Total hip replacement	Nonsmoker
11	62	M	80.0	2	175	Hemiarthroplasty	Smoker
12	63	M	67.7	3	100	Colostomy revision	Smoker
13	65	M	64.5	2	150	Abdominal perineal resection	Smoker
14	65	M	69.1	2	156	Cholecystectomy	Smoker
15	70	M	110.0	2	151	Hemicholectomy	Nonsmoker

the operating room suite at the Health Sciences Centre early in the morning after an overnight fast. Subjects had intravenous catheters placed in each forearm, one for drug infusion, and the other in an antecubital vein for removal of blood samples after administration of the drug dose. The latter cannula was kept patent by a heparin in saline solution ($10\ U \cdot ml^{-1}$). After discarding the first 3 ml, a 10 ml blood sample was withdrawn and placed in a glass tube containing sodium oxalate as the anticoagulant. Plasma was separated by centrifugation and frozen at −20° C until subsequently analyzed for alfentanil concentration. The drug dose ($20\ \mu g \cdot kg^{-1}$) was infused by pump over one minute, and blood samples for drug analyses were taken prior to the drug dose and at 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240 and 300 minutes after the end of the drug administration. Subjects remained supine throughout the study.

Surgical patients protocol

Male patients presenting to the Veterans Administration Hospital for elective surgical procedures consented to have alfentanil pharmacokinetics determined during their surgical procedure. All patients were premedicated with cimetidine, 300 mg, morphine, 8–12 mg, and a benzodiazepine, diazepam 5–10 mg or lorazepam 1–4 mg. Anaesthesia was induced with IV alfentanil (100–180 $\mu g \cdot kg^{-1}$ given over one minute by infusion pump, and a neuromuscular blocking agent was administered immediately after anaesthetic induction. The anaesthetic dose of alfentanil was reduced primarily in older patients or in those with a higher ASA rating. Induction of anaesthesia was performed by one of two anaesthetists, and was similar for all patients. Ethical considerations influenced subsequent procedures and the protocol allowed for some variation. Anaesthesia was supplemented with thiopentone, 50–250 mg, in five patients who were judged to be inadequately anaesthetised when there was a rapid heart rate, increase in blood pressure and/or excessive high frequency activity on the computerized EEG monitor at the end of alfentanil infusion. All patients received either pancuronium ($0.025–0.10\ mg \cdot kg^{-1}$) and/or succinylcholine ($1.5\ mg \cdot kg^{-1}$) prior to tracheal intubation. In situations where there was a risk of gastric aspiration or where the procedure was of short duration, muscle relaxation was produced with succinylcholine. Otherwise, appropriate doses of either pancuronium or pancuronium/ metocurine were administered, and surgical anaesthesia was maintained with the addition of nitrous oxide, 40–60 per cent, in all subjects and with isoflurane, 0.25–2 per cent, in four of them. Blood samples for alfentanil analysis were taken from an indwelling arterial cannula prior to the drug dose and at 2, 4, 6, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes after the end of the alfentanil dose. Plasma was separated by centrifugation, frozen and shipped to the Clinical Pharmacology Laboratories at the University of Manitoba for quantitation of alfentanil. All samples were stored at −20° C until analyzed.

Quantitation of alfentanil in plasma

Plasma samples were extracted according to Phipps *et al.*[17] Fentanyl free base, 100 ng/sample, was the internal standard. Alfentanil was quantified by gas–liquid chromatography using a Hewlett-Packard model 5710 instrument equipped with a nitrogen/phosphorus detector. Chromatographic conditions were as described by Gillespie *et al.*[18] All samples were subject to duplicate analyses. The

TABLE II Pharmacokinetic disposition characteristics for alfentanil administered as a rapid IV infusion to young (YS) and old (OS) healthy subjects and to young (YP), middle aged (MP) and old (OP) surgical patients. Data are presented as means ± SEM and were transformed before statistical analyses when Bartlett's test indicated nonhomogeneity of variance

	YS	*OS*	*YP*	*MP*	*OP*
N	*10*	*10*	*4*	*6*	*5*
Age (yr)	26 ± 1	65 ± 4	32 ± 7	52 ± 5	65 ± 3
Weight (kg)	70.2 ± 5.2	74.6 ± 3.3	71.7 ± 5.9	85.1 ± 5.5	78.4 ± 8.3
α (min^{-1})	0.438 ± 0.076	0.877 ± 0.537	0.282 ± 0.048	2.75 ± 1.79	0.398 ± 0.148
β (min^{-1})	0.021 ± 0.004	0.014 ± 0.002	0.097 ± 0.063[a]	0.035 ± 0.009[b]	0.010 ± 0.007
Vss ($L \cdot kg^{-1}$)	0.391 ± 0.056	0.340 ± 0.077	0.554 ± 0.130	0.434 ± 0.090	0.404 ± 0.040
Vp ($L \cdot kg^{-1}$)	0.270 ± 0.047	0.257 ± 0.068	0.225 ± 0.079	0.339 ± 0.064	0.280 ± 0.027
Vc ($L \cdot kg^{-1}$)	0.131 ± 0.028	0.083 ± 0.011	0.329 ± 0.079[c]	0.096 ± 0.034	0.125 ± 0.032
Clp ($ml \cdot kg^{-1} \cdot min^{-1}$)	9.3 ± 2.0	4.1 ± 0.8	39.6 ± 19.0[d]	12.8 ± 2.5	4.6 ± 1.6[e]
ke (min^{-1})	0.092 ± 0.019	0.062 ± 0.014	0.124 ± 0.064	0.282 ± 0.109	0.098 ± 0.097

[a]Greater than OS and OP.
[b]Greater than OP.
[c]Greater than all other groups.
[d]Greater than all others excepting MP.
[e]Less than YP and MP.
Vss, volume of distribution at steady-state; Vp, peripheral compartment volume; Vc, central compartment volume; Clp, plasma clearance; ke, elimination rate constant.

coefficient of variation for analyses of plasma concentrations between 20 and 1600 $ng \cdot ml^{-1}$ was 6.6 per cent, and 11.0 per cent for concentrations between 1.2 and 20 $ng \cdot ml^{-1}$.

Data analyses

Standard curves for quantitation of alfentanil were derived by unweighted least squares linear regression analysis of peak area ratio of alfentanil:fentanyl versus added alfentanil concentration in spiked plasma samples. Plasma drug concentrations from subjects receiving alfentanil were determined from these standard curves. Plasma concentration versus time data were fitted to a two-compartment open model with first order rate constants, taking into account the one-minute drug infusion time, using the pharmacokinetic analysis program PCNONLIN.[19] Kinetic constants as a function of age, sex and health status were analyzed by analysis of variance using the program package SYSTAT.[20] Homogeneity of data distribution was assessed by Bartlett's test. Data which were not normally distributed were log-transformed to produce homogeneity of variance prior to statistical analyses. Multiple comparisons were made with Duncan's test. Significant differences were accepted when $P \leq 0.05$. Data in the text are presented as means ± SD.

Results

Subjects were grouped by age for comparison of the pharmacokinetic characteristics of alfentanil in healthy volunteers and in surgical patients. Subjects were classified as young if less than 40 years, middle-aged from 40 to 60 years, and old if beyond 60 years of age. This resulted in two groups, young and old for the healthy volunteers, and three groups for the surgical patients.

The plasma concentration versus time data were very well fitted by the two-compartment model (r = 0.97 ± 0.04). Comparison of the pharmacokinetic characteristics of alfentanil among these groups of subjects is presented in Table II. The initial drug distribution into the peripheral kinetic compartment, alpha (half-time, 0.06–19.25 min, median 2.11 min) was not different with respect to age or health status. This finding was also true for apparent volume of distribution at steady-state (Vss), and for the peripheral compartment space (Vp). However, the volume of the central compartment (Vc) was larger in young surgical patients than in any other group of subjects ($P = 0.013$). Regression analysis of Vc versus age (Figure 1) indicated a significant decline with a modest inverse correlation ($r = -0.323$, $P < 0.05$). Kinetic constants associated with the elimination process showed significant differences among groups for β ($P = 0.039$) (half-time 8–693 min, median 41 min) and plasma clearance (Clp) ($P < 0.001$) but not for the elimination rate constant (ke) ($P = 0.151$). The Clp was significantly reduced in the elderly healthy subjects and surgical patients, and regressions of β and Clp versus age showed a significant decline with age (Figures 2 and 3).

Analysis of data showed no significant association of smoking on alfentanil disposition. Also, in the healthy volunteers who received the 20 $\mu g \cdot kg^{-1}$ dose, there was no difference associated with the sex of the subjects. It is of interest that the five patients requiring thiopentone in addition to alfentanil for the induction of anaesthesia had

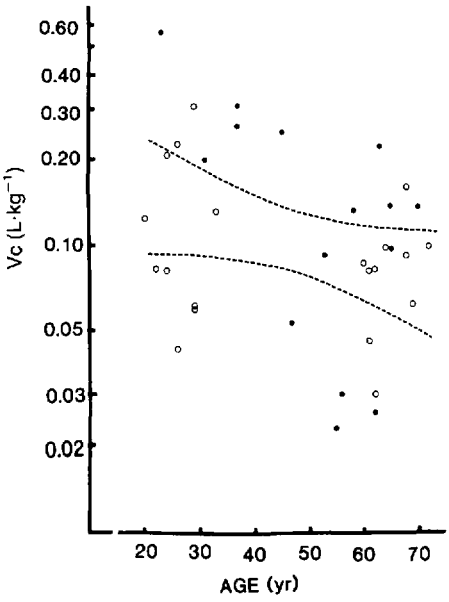

FIGURE 1 Relationship between age and central compartment distribution volume (Vc) in healthy volunteers (○) and in surgical patients (●) receiving an IV dose of alfentanil. The dashed lines indicate the 95 per cent confidence interval for the association ($F_{1,33}$ = 3.84, $P < 0.05$, $r = -0.32$). Data were log-transformed before statistical analysis since the raw data did not satisfy Bartlett's test for homogeneity of variance.

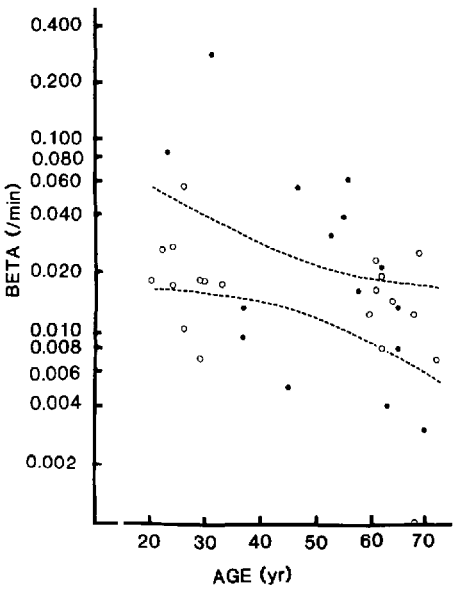

FIGURE 2 Relationship between age and the β disposition rate constant in healthy volunteers (○) and in surgical patients (●) who received an IV dose of alfentanil. The dashed lines indicate the 95 per cent confidence interval for the association ($F_{1,33}$ = 5.88, $P < 0.01$, $r = -0.39$). Data were log-transformed before statistical analysis since the raw data did not satisfy Bartlett's test for homogeneity of variance.

higher elimination rates for alfentanil than pooled data from all other subjects, as reflected by β (0.043 ± 0.014 · min^{-1}, P = 0.034), ke (0.261 ± 0.135 min^{-1}, P = 0.023) and Clp (25.1 ± 14.8 ml · $min^{-1} \cdot kg^{-1}$, P = 0.018). The four patients who received isoflurane anaesthesia did not receive thiopentone and were not different from the remaining subjects in their kinetic disposition of alfentanil.

Discussion

Description of alfentanil disposition has involved both two- and three-compartment kinetic models,[2] and some uncertainty exists as to which model should be preferred.[14,15] Since our data showed excellent concordance with the two-compartment model when we factored in the infusion time, and this involved invoking only one kinetic space from which no direct drug measurements are possible, we chose the two-compartment model with correction for drug infusion time. The fact that much of the kinetic data for alfentanil disposition is not normally distributed is appreciated by investigators who have studied its disposition.[14] In our study, only Vss and Vp showed homogeneity of variance as indicated by Bartlett's test. All other kinetic data were log-transformed to produce homogeneity of variance so that parametric statistical analyses would be valid.

Our values for the alpha disposition constant are somewhat greater than described in most other studies utilizing a two-compartment model, but are similar to values for pi, the initial most rapid disposition constant, where the three-compartment model was used.[2,3] Some of the difference is undoubtedly due to the lack of correction for drug infusion time by most investigators. Our estimates for Vss, Vp and Vc are similar to other reports in the literature[3,4,6–9,12,13,15] and our finding of a significant but modest reduction of Vc with age confirms the report by Scott and Stanski.[15]

Disposition constants relevant to elimination, includ-

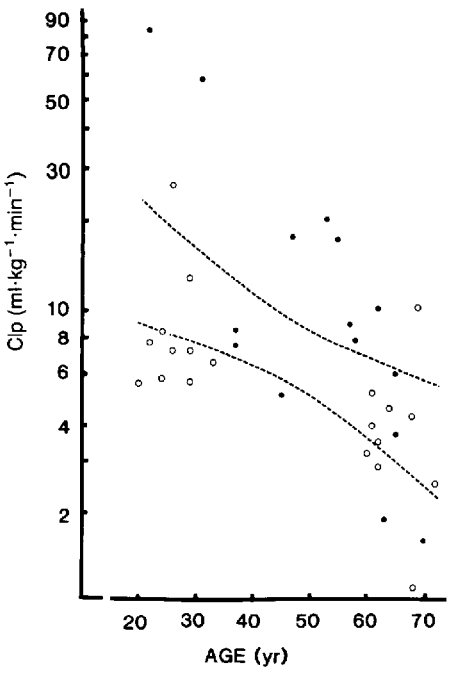

FIGURE 3 Relationship between age and plasma clearance (Clp) of alfentanil in healthy volunteers (○) and in surgical patients (●) who received an IV drug dose. The dashed lines indicate the 95 per cent confidence interval for the relationship ($F_{1,33} = 12.40$, $P = 0.001$, $r = -0.54$). Data were log-transformed before statistical analysis since the raw data did not satisfy Bartlett's test for homogeneity of variance.

ing Clp, β and ke, were highly variable in our cohort, and exceeded previously reported values for some of our study subjects, especially in the young surgical patient group.[2,3,6,11,14,15] The inconsistency in finding age-associated reduction in Clp is undoubtedly related to the nonlinear relationship in this disposition constant with age.[14] The use of half-time for these comparisons is inappropriate, since it is not a normally distributed kinetic variable. This is the first study to examine smoking as a factor contributing to interindividual variance in elimination. The finding that variance is much greater for younger subjects (Figure 3) suggests some environmental factor may be inducing alfentanil clearance in this group of patients. It is possible that this environmental stimulus could be surgical stress, since the nature of the surgical intervention varied considerably among our study subjects, but this factor has only been pursued in animal studies.[21] This interpretation requires further study due to the small number of young surgical patients with the highest clearance values, Table II. Our finding that patients requiring thiopentone supplementation of anaesthesia had higher clearances of alfentanil than the remainder of the subjects is of interest and suggests that resistance to alfentanil anaesthesia is likely to include a major drug metabolic component. The lack of effect of isoflurane on alfentanil pharmacokinetic disposition has been reported previously.[14]

In conclusion, this is the first concurrent comparison of the kinetic disposition of alfentanil in young and old healthy volunteers with surgical patients. The kinetic data from this study, derived from gas chromatographic analysis of plasma for alfentanil, are consistent with similar data where radioimmunoassay was the analytical technique. Our data suggest that older patients metabolize alfentanil more slowly than their younger counterparts and that smoking of tobacco does not contribute to this variation. The more consistent disposition characteristics for alfentanil in elderly subjects suggest that dose–response relationships will be the most predictive in patients older than 60 years, and that surgical stress does not have a significant effect on alfentanil kinetics in this older group.

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Résumé

On a étudié la disposition pharmacocinétique de l'alfentanil chez 20 volontaires en bonne santé et chez 15 patients chirurgicaux âgés de 20 à 72 ans. La disposition pharmacocinétique était du premier ordre et était bien décrite par le modèle ouvert à deux compartiments. Le volume du compartiment central de distribution était de $0.131 \pm 0.028\ L \cdot kg^{-1}$ *(moyenne ± SM) chez des patients volontaires en bonne santé et diminuant légèrement avec l'augmentation de l'âge (*$r = -0.32$, $P < 0.05$*). Cependant, le volume apparent de distribution après équilibration était de* $0.404 \pm 0.035\ L \cdot kg^{-1}$ *pour tous les patients de l'étude et n'était pas en relation avec l'âge. La clearance plasmatique de l'alfentanil chez des sujets jeunes en bonne santé était de* $9.3 \pm 2.0\ ml \cdot kg^{-1} \cdot min^{-1}$*, a aussi démontré une relation inverse avec l'âge (*$r = 0.54$, $P < 0.001$*), et n'était pas affectée par le stress chirurgical chez les sujets plus âgés que 60 ans. Le tabagisme et le sexe des sujets n'a pas contribué à des différences dans la disposition de cette drogue. On a trouvé que les différences entre les individus dans la disposition de l'alfentanil étaient moindres chez les sujets âgés suggérant que ses effets pharmacologiques reliés à la disposition pharmacocinétique doivent être plus prévisibles chez les gens âgés.*