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Decreased Fentanyl and Alfentanil Dose Requirements with Age. A Simultaneous Pharmacokinetic and Pharmacodynamic Evaluation[1]

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ABSTRACT

The effect of increasing age on the dose of fentanyl or alfentanil required to produce the same electroencephalographic (EEG) stage was studied in adult male patients. The pharmacokinetic and pharmacodynamic components of each patient's dose-response relationship were evaluated simultaneously. Frequent arterial blood samples drawn during and after an infusion of fentanyl or alfentanil were assayed by radioimmunoassay and permitted determination of each patient's pharmacokinetic profile. The EEG was analyzed by power spectral analysis and a parameter (spectral edge frequency) chosen to quantitate the narcotic-induced EEG slowing. An inhibitory sigmoid E_{max} pharmacodynamic model related spectral edge frequency to narcotic serum concentrations. The dose requirement of fentanyl or alfentanil decreased significantly with increasing age (a 50% decrease from age 20 to 89). No age-related changes in the pharmacokinetic parameters were found. Brain sensitivity (as determined by EEG changes) did decrease significantly with age. Thus, the decreased dose requirement in the elderly had a pharmacodynamic explanation, using the EEG as a measure of narcotic drug effect.

The elderly population in America increases annually, and, by 2039, the segment of our population over 65 will number almost 52 million (Vestal, 1979). It is estimated that over 50% of this population will have a surgical procedure before death. Many of these patients will receive narcotics for perioperative care. Although clinical experience has long dictated that elderly patients require less narcotic than young patients, the reasons for a decreased dose requirement are not clear. One explanation may be age-related changes in pharmacokinetics (drug distribution and metabolism), pharmacodynamics (the response of a patient to a given plasma concentration of drug) or both.

Belleville *et al.* (1971) reported that the degree of pain relief obtained with i.m. morphine or pentazocine correlated positively with age. Kaiko (1980) also reported increased analgesia with i.m. morphine in elderly patients. Although these studies documented decreased dose requirements (for postoperative analgesia), neither pharmacokinetic nor pharmacodynamic evaluations were possible. Berkowitz *et al.* (1975) reported that older patients had higher morphine serum concentrations at 2 and 5 min after i.v. administration but detected no other pharmacokinetic differences between young and old patients. In a more recent study, Owen *et al.* (1983) found that morphine in older patients had a lower clearance and smaller steady-state volume of distribution and a shorter terminal elimination half-life than in younger volunteers. Their clearance results (27.7 ml/kg/min in elderly patients and 33.7 ml/kg/min in young patients) were considerably higher than values reported by other investigators (Stanski *et al.*, 1978, 12.4 ml/kg/min in the elderly and 14.7 ml/kg/min in the young; Säwe *et al.*, 1981, 9.2 ml/kg/min in adults aged 49–75). No explanation for their high clearance values was offered.

Chan *et al.* (1975) compared the plasma levels of i.m. meperidine in anesthetized young and old patients and found that older patients had higher plasma concentrations after equivalent doses calculated on body weight. No formal kinetic or dynamic analysis was performed. They surmised that both decreased distribution and decreased metabolism contributed to higher concentrations in the elderly. The dose requirement with varying age was not evaluated.

The kinetics of fentanyl in the elderly were reported by Bentley *et al.* (1982). In older patients, fentanyl had considerably longer elimination half-lives due to lower clearances. Volumes of distribution were unchanged. Their results are questionable, however, because their sampling duration of 420 min was considerably shorter than the 945 min elimination half-life they reported for the elderly. No assessment of dose requirement or drug effect was made.

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ABBREVIATION: EEG, electroencephalographic.

The kinetics of alfentanil in young and old was investigated by Helmers *et al.* (1984). In their older patients, alfentanil demonstrated lower clearances, unchanged initial and steady-state volumes of distribution and longer terminal elimination half-lives. They attributed lower clearances to decreased metabolism in the elderly. Again, no assessment of dose requirement or pharmacodynamic effect was made.

Thus, a number of studies have demonstrated age-related changes in the dose requirement for morphine without attempting a pharmacokinetic or dynamic explanation. The pharmacokinetic studies that are available for morphine, meperidine, fentanyl and alfentanil do not combine assessments of dose requirement with age or pharmacodynamics. The study of age-related "sensitivity" to narcotics needs to be done by simultaneously measuring both pharmacokinetic and pharmacodynamic parameters. The difficulty in assessing narcotic effect in a quantifiable, continuous manner has no doubt hampered attempts to do so.

To measure narcotic effect, we used power spectral analysis of the EEG changes induced by fentanyl or alfentanil. We have shown previously that the spectral edge frequency of the EEG power spectral analysis can provide a continuous, noninvasive quantitation of the cerebral effects of these two opiates (Scott *et al.*, 1985). Serum concentrations of fentanyl or alfentanil were determined simultaneously to assess the pharmacokinetic parameters in each patient. The present study was designed to determine whether aging decreases fentanyl or alfentanil dose requirements in surgical patients and whether altered dose requirements can be attributed to changes in pharmacokinetics, pharmacodynamics or both.

Methods

Patient population. After Institutional Review Board approval and informed consent, 37 patients were given either fentanyl ($N = 20$, ages 20–88) or alfentanil ($N = 17$, ages 20–89). All patients were males, American Society of Anesthesiologists physical status I or II, scheduled for elective surgery with minimal expected blood loss. They were free of significant obesity and neurological, cardiac, pulmonary, renal or hepatic disease. None had a history of narcotic or ethanol abuse. None were given any drug affecting the central nervous system for 24 hr before the study.

Conduct of the study. Each unmedicated patient was brought to the operating room, where i.v. and arterial catheters were placed in contralateral arms. EEG electrodes were placed on each patient's scalp in the following configuration: FP1, FP2, O1, O2 and CZ (international 10/20 system of electrode placement) (Jasper, 1958); FP = frontoparietal, CZ = vertex of head, O = occipital, 1 = left and 2 = right. In addition, a ground electrode was placed in the midline of the patient's forehead. The following channels were recorded: FP-O1, FP2-O2, CZ-O1 and CZ-O2. The EEG was recorded on a Beckman Accutrace and simultaneously stored on magnetic tape using a Vetter model A tape recorder for subsequent off-line analysis. Direct arterial blood pressure and heart rate were continuously displayed and their values recorded every 30 sec.

Glycopyrrolate, 0.2 mg, and pancuronium, 1 mg, were administered i.v. A mask was lightly applied to the patient's face and pure oxygen delivered *via* a nonrebreathing system. Narcotic infusion was started after a 5-min base-line EEG recording taken with the patient resting quietly (eyes closed). Patients' responsiveness to commands was assessed every 30 sec by a request to open eyes or move toes. With the loss of response to verbal command, a succinylcholine infusion of 1 mg/min was started to attenuate or eliminate chest wall rigidity and electromyographic artifacts in the EEG recording. Ventilation was continuously monitored and assisted as indicated clinically. Arterial blood gases were checked within 2 min of terminating narcotic infusion to assess adequacy of ventilation.

Fentanyl was infused at 150 μg/min and alfentanil at 1500 μg/min. Narcotic infusion for each patient was terminated with the appearance of δ wave activity in the raw EEG tracing. δ Waves were defined as having a frequency of $\leq$4Hz and an amplitude of $\geq$50 μV. Succinylcholine infusion was terminated when δ waves disappeared from the EEG during the recovery phase. EEG recording continued until patients were alert and the EEG signal had returned to base line. This occurred in 30 to 45 min.

After the EEG portion of the study was concluded, anesthesia was induced with thiopental. Succinylcholine was used to facilitate tracheal intubation, and anesthesia was maintained with nitrous oxide and enflurane as clinically necessary for the patient's surgery.

Arterial blood samples were drawn at 0.5- to 1-min intervals during the infusion and at 2- to 4-min intervals thereafter until EEG recording stopped. Blood samples were then drawn every 1 to 2 hr (including the period of surgery) for a total of 24 hr for fentanyl or 12 hr for alfentanil. Approximately 40 samples were drawn from each patient. Each sample was allowed to clot and then centrifuged promptly. The serum was separated and frozen at −20°C until analyzed by radioimmunoassay for narcotic serum concentration (Michiels *et al.*, 1977, 1983). The fentanyl assay was sensitive to 0.25 ng/ml and the alfentanil assay to 1.0 ng/ml. Day-to-day variability was 8% at 24 ng/ml and 13% at 3 ng/ml for fentanyl, 14% at 100 ng/ml and 17% at 20 ng/ml for alfentanil. Within days, variability was 4% at 3 and 24 ng/ml for fentanyl and 10% at 20 and 100 ng/ml for alfentanil.

Pharmacokinetic data analysis. Bi- and triexponential models were fit to the narcotic serum concentration *vs.* time data using an extended least-squares nonlinear regression technique (Peck *et al.*, 1984). For each patient, the log likelihood values of the two fits were examined using the chi square distribution with $P < .05$ to determine which model was statistically preferred (Sheiner, 1981). Model-dependent standard formulae were used to derive the pharmacokinetic parameters of interest (Gibaldi and Perrier, 1982).

Pharmacodynamic data analysis. The EEG stored on magnetic tape was analyzed off-line by a Digital PDP 11/23 computer (Digital Equipment Corporation, Maynard, MA). The EEG signal was divided into 5-sec epochs, and the analog signal was digitized at 100 Hz with 10-bit resolution. The digital data were subjected to fast Fourier analysis to determine the frequencies and amplitudes present in each epoch. Fast Fourier analysis resolves the complex EEG wave form into its component sine and cosine waves of known frequency and amplitude. Frequencies above 35 Hz were not used, as electromyographic artifact was the overwhelming source of "EEG" activity above this frequency.

The amplitudes for each frequency band (0.4 Hz in width) from 0.4 to 35 Hz were then squared to obtain power and construct a power *vs.* frequency histogram for each epoch. The spectral edge frequency was then determined for each epoch by calculating the area under the power *vs.* frequency histogram and determining which frequency and 95% of the area of the histogram below it (Rampil *et al.*, 1980). The spectral edge frequency can characterize the degree of overall frequency slowing seen in the EEG. As the predominant frequencies slow, the spectral edge frequency will decrease. Noise present in the spectral edge frequency data was decreased by a curve-smoothing technique that represents each spectral edge frequency value by the mean of the five previous and five subsequent spectral edge frequency values (Scott *et al.*, 1985).

Pharmacodynamic modeling. The spectral edge frequency values were related to the narcotic serum concentration values by unweighted least-squares nonlinear regresssion (Sheiner, 1981) using the following pharmacodynamic model: $SE(t) = Eo - \{E_{max} \cdot Ce(t)^{\gamma}/[IC_{50}^{\gamma} + Ce(t)^{\gamma}]\}$, where SE (t) is the spectral edge frequency value (hertz) at time t; Eo is the base-line spectral edge frequency (hertz); E_{max} is the maximal decrease in spectral edge frequency (hertz) produced by the narcotic; Ce(t) is the concentration of the narcotic in the effect compartment (nanograms per milliliter) at time t; IC_{50} is the steady-state fentanyl or alfentanil serum concentration (nanograms per milliliter) that produces

half the maximal spectral edge frequency decrease; γ is a dimensionless number reflecting the sigmoidicity of the curve. This pharmacodynamic modeling was performed using each patient's pharmacokinetic parameters obtained from the pharmacokinetic fits as constants.

The IC_{50} parameter characterizes individual patient brain sensitivity to the narcotic (based on EEG changes) at steady-state conditions. It is independent of pharmacokinetic considerations.

The incorporation of an effect compartment concept is necessary because the spectral edge frequency data lag behind the serum narcotic concentration data, and this precludes a direct relationship (Scott *et al.*, 1985). The effect site of the narcotic is postulated to be in a separate "effect" compartment (Holford and Sheiner, 1981). The intensity of the narcotic effect (spectral edge frequency changes) is linked directly to the concentration in the effect compartment [Ce(t)]. A first-order rate constant (Keo) characterizes the temporal aspects of equilibration between the serum concentration and the effect compartment concentration. Thus, Keo or its equivalent, $T_{\frac{1}{2}}$Keo (0.693/Keo), quantitates the magnitude of the temporal lag or equilibration delay between changes in serum narcotic concentration and narcotic effect.

An independent reviewer (with no knowledge of the doses or times of narcotic administration) determined from the raw EEG records the point of first appearance of δ waves (defined as waves with an amplitude greater than 50 μV and a frequency less than 4 Hz). This time was multiplied by the respective infusion rate to determine the "EEG dose" administered to each patient. The narcotic infusion was terminated when the δ waves were well established in the raw EEG tracing and maximal EEG slowing was assured. Therefore, the total dose was greater than the dose needed only to achieve δ waves in the raw EEG tracing (the EEG dose).

Age-related statistical analysis. Linear regression was used to relate the pharmacokinetic and dynamic parameters of the patients with age using the BMDP statistical package (1983 edition). The statistical significance of the correlations with age was tested using the F statistic, and the slope of each regression line was tested for statistical significance (different from zero slope) with a t test. A P value $< .05$ was considered statistically significant. Harmonic means were calculated for half-lives and standard deviations of harmonic means calculated according to Lam *et al.* (1985).

Results

Comparisons between fentanyl and alfentanil. The age ranges in both narcotic groups were similar (tables 1 and 2). Age did not significantly correlate with weight in either drug group. Both fentanyl and alfentanil caused similar EEG changes; representative EEG changes are shown in figure 1. The mean ± S.D. dose required to reach δ waves was higher for alfentanil (3898 ± 2280 μg) than for fentanyl (771 ± 414 μg).

The pharmacodynamic parameter estimates (tables 1 and 2) show that both narcotics caused similar maximal decreases in spectral edge frequencies (E_{max}) starting from similar base-line values for spectral edge frequences (Eo). Representative spectral edge values *vs.* time plots for young and old patients are shown in figures 2 and 3. The similarity of Eo and E_{max} values can be seen. γ Values were also similar for fentanyl and alfentanil.

The fentanyl group had a significantly greater time lag between narcotic serum concentration changes and spectral edge frequency response ($T_{\frac{1}{2}}$Keo for fentanyl, 4.7 *vs.* 0.9 min for alfentanil). This time lag is seen in figure 2, especially in the young patient, where the spectral edge value remains unchanged from base line for approximately 5 min, despite the rapid increase in serum fentanyl concentrations. In contrast, the patients given alfentanil (fig. 3) show spectral edge frequencies that changed more rapidly in response to the increase in serum alfentanil concentrations.

TABLE 1

Fentanyl dose requirement and pharmacodynamic parameters

EEG dose, dose delivered to patient when δ waves were first detected in raw EEG; Eo, base-line spectral edge value; E_{max}, maximal decrease in spectral edge value in each patient from base line; IC_{50}, steady-state fentanyl concentration associated with 50% decrease in spectral edge; $T_{\frac{1}{2}}$ Keo, half-time of equilibration between central compartment and effect site of fentanyl concentrations; δ, dimensionless number describing the sigmoidicity of the serum concentration-effect curve.

Age	EEG Dose	Eo	E_{max}	IC_{50}	$T_{\frac{1}{2}}$ Keo	γ
yr	*μg*	*Hz*	*Hz*	*ng/ml*	*min*	–
20	949	18.0	9.4	9.3	4.6	4.7
23	1129	15.2	7.2	13.4	2.8	3.3
33	1428	19.3	8.6	7.8	3.5	2.1
33	1113	23.1	15.9	9.8	6.5	5.1
34	1824	20.0	13.4	10.2	5.9	4.4
51	465	18.9	15.2	7.4	6.1	5.2
52[a]	788	15.7	13.8	7.8	3.8	1.4
56	592	22.2	15.2	5.9	8.5	5.8
57[a]	492	17.4	12.9	6.3	4.6	5.2
57	526	19.2	16.1	9.6	5.6	3.3
64	592	18.8	11.2	5.8	6.8	5.8
64[a]	319	16.9	12.1	4.1	3.3	5.6
67	597	18.3	14.0	6.2	7.0	3.9
77	565	20.3	12.3	6.2	5.0	5.1
80[a]	435	19.2	14.8	3.8	4.2	3.7
88	517	19.4	15.4	11.3	4.0	4.2
Mean	717*	18.9	13.0	7.8*	4.7*[b]	4.3
S.D.	414	2.1	2.7	2.6	1.5	1.3

[a] Patient not in table 3.
[b] Harmonic mean.
* Significantly different from alfentanil values, table 2 ($P < .001$).

TABLE 2

Alfentanil dose requirement and pharmacodynamic parameters

EEG dose, dose delivered to patient when δ waves were first detected in raw EEG; Eo, base-line spectral edge value; E_{max}, maximal decrease in spectral edge value in each patient from base line; IC_{50}, steady-state alfentanil concentration associated with 50% decrease in spectral edge; $T_{\frac{1}{2}}$ Keo, half-time of equilibration between central compartment and effect site of alfentanil concentrations; γ, dimensionless number describing the sigmoidicity of the serum concentration-effect curve.

Age	EEG Dose	Eo	E_{max}	IC_{50}	$T_{\frac{1}{2}}$ Keo	γ
yr	*μg*	*Hz*	*Hz*	*ng/ml*	*min*	–
20	4755	12.9	5.2	819	0.8	3.8
23	7620	17.3	9.0	349	0.8	2.0
23	10500	17.8	14.5	1190	0.8	7.3
29	3330	22.6	17.4	478	0.9	2.6
32	2970	21.0	13.1	581	0.9	3.6
33	3870	24.3	18.3	563	1.4	6.6
51	3855	18.8	13.7	717	1.0	5.4
51	3480	20.8	14.5	401	0.7	5.8
61	5100	14.5	9.4	676	0.9	4.9
66	3195	19.4	14.9	289	1.6	3.7
69	2745	17.5	9.6	329	0.5	6.2
73	1995	21.7	16.1	136	1.1	1.5
74	1650	14.9	8.7	227	0.6	10.0
77	2505	21.7	16.7	251	1.7	3.0
77	2550	24.8	20.5	280	1.4	8.1
89	2250	18.0	14.7	375	1.1	2.5
Mean	3898*	19.2	13.5	479*	0.9*[a]	4.8
S.D.	2280	3.4	4.1	271	0.3	2.4

[a] Harmonic mean.
* Significantly different from fentanyl values, table 1 ($P < .001$).

The mean steady-state narcotic concentration causing half the maximal spectral edge frequency decrease (IC_{50}) differed significantly for the two narcotics. For fentanyl, the mean concentration was 7.8 ng/ml, whereas 479 ng/ml were required for alfentanil.

Fentanyl was detectable in the serum of 12 patients for 22 to 24 hr, in three patients for 12 to 15 hr, in two patients for 8 to

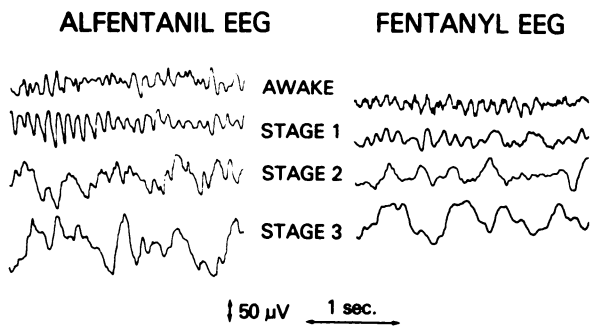

Fig. 1. EEG stages for fentanyl and alfentanil. Representative 3-sec tracings of EEG recordings from fentanyl and alfentanil are shown. Awake = mixed α (8–13 Hz) and β (>13 Hz) activity. Stage 1 = slowing with α spindles. Stage 2 = more slowing, θ activity present (4–7 Hz). Stage 3 = maximal slowing, δ waves present (<4 Hz), with high amplitude.

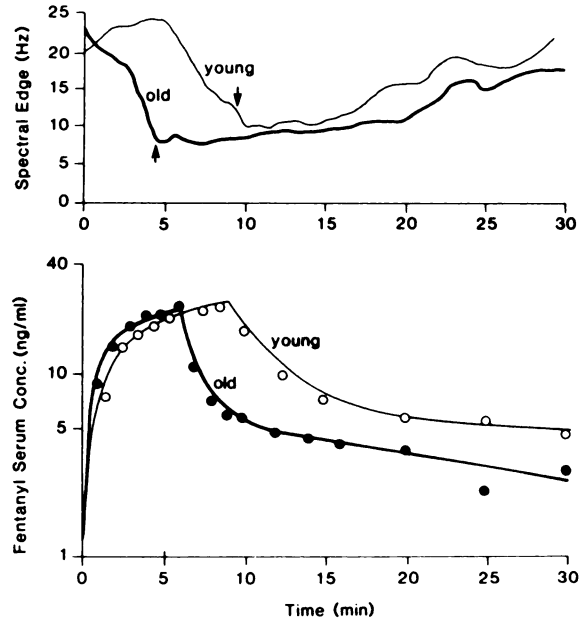

Fig. 2. Fentanyl serum concentrations and spectral edge values *vs.* time. Representative changes with time are shown for a young patient (age 33; thin lines, O) and an old patient (age 77; thick lines, ●). The arrows in the upper half represent the time when δ waves first appeared in the raw EEG. The circles are measured fentanyl concentrations and the solid lines the predicted concentrations. The younger patient lags behind, in effect, despite serum concentrations approximately the same as the older patient. Although the same "driving force" exists for both patients, given the time lag between serum concentration changes, the concentration changes in the brain and the lower IC_{50} for older patients, the older patients reach the maximal effect sooner. Conc., concentration.

10 hr and in three patients for 6 to 8 hr. Alfentanil was detectable in the serum of nine patients for 12 hr, in six patients for 10 to 12 hr and in two patients for 8 to 10 hr.

The pharmacokinetic analysis reveals major differences between the volumes of distribution and clearance rates of fentanyl and alfentanil (tables 3 and 4). The initial and steady-state volumes of distribution (V_1 and Vd_{ss}) of alfentanil are almost 1/10 that of fentanyl. The total body clearance of alfentanil is approximately one-third that of fentanyl. The terminal elimination half-life of alfentanil is significantly shorter (118 min) than that of fentanyl (475 min). The pharmacokinetic characterization of the early distribution phases of the serum concentration *vs.* time curves appears in the bottom halves of figures 2 and 3. Representative serum concentration *vs.* time curves for the two narcotics are indicated in figure 4. The elimination phase is well characterized in these figures. In all

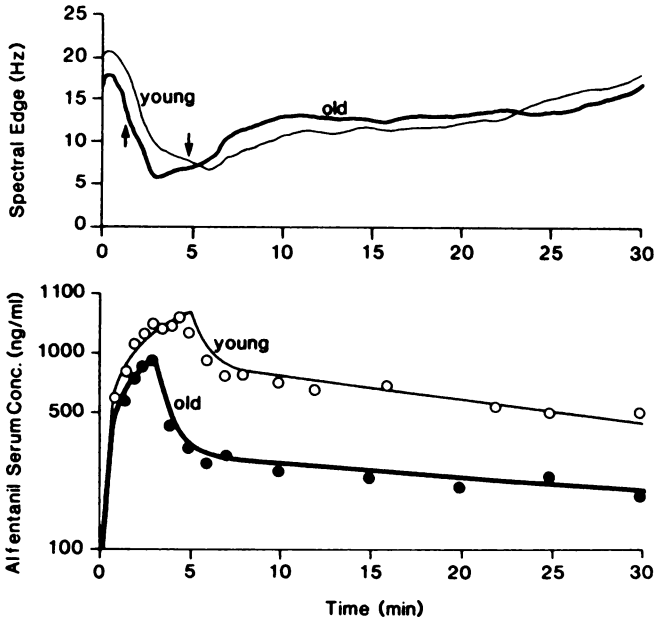

Fig. 3. Alfentanil serum concentrations and spectral edge values *vs.* time. Representative changes with time are shown for a young patient (age 32, thin lines, O) and an old patient (age 89, thick lines, ●). The arrows in the upper half represent the time when δ waves first appeared in the raw EEG. The circles are measured alfentanil concentrations and the solid lines the predicted concentrations. The young patient requires a higher serum concentration to reach the same EEG endpoint. The EEG effects track the serum concentrations closely, and the older patient requires a lower brain concentration and thus a lower serum concentration at maximal effect. Conc., concentration.

patients, a triexponential model optimally characterized the data and was statistically preferred.

No pharmacokinetic parameter correlated significantly with weight, including initial and steady-state volumes of distribution and total body or intercompartmental clearances.

Dose requirements *vs.* age. The narcotic dose required to produce the same EEG endpoint (first appearance of δ waves in the raw EEG) showed a significant negative correlation with age (fig. 5): for fentanyl, $r = -0.72$ ($P < .005$); for alfentanil, $r = -0.67$ ($P < .005$). The regression relationships with age are indicated in the legend to figure 5. The older patients required significantly lower doses. The comparative doses given to these representative young and old patients can be seen in figures 2 and 3. The arrows in the top halves of the figures indicate the time that δ waves first appeared in the raw EEG tracing (the EEG dose), which is less for the older patients.

Pharmacodynamic parameters *vs.* age. The IC_{50} values decreased significantly with increasing age for both fentanyl and alfentanil (fig. 6). The correlation coefficients were fentanyl, $r = -0.52$ ($P < .05$), and alfentanil, $r = -0.66$ ($P < .005$). From age 20 to 85, the IC_{50} values decreased approximately 50%. Moderate variability in this parameter is evident, and the outlier IC_{50} value for an 88-year-old fentanyl patient can be seen (not excluded from analysis). The regression equations are indicated in the legend to figure 6. The other pharmacodynamic parameters, $T_{1/2}Keo$, Eo, E_{max} and γ, did not have age-related changes.

Pharmacokinetic parameters *vs.* age. The pharmacokinetic parameters for both fentanyl and alfentanil, with a few exceptions, lacked important changes with age. In particular, the correlation coefficients of the initial distribution volume *vs.* age were 0.04 (fentanyl) and −0.31 (alfentanil). Distribu-

TABLE 3
Fentanyl pharmacokinetic parameters

Age	Distribution Half-Lives		Elimination Half-Life	V_1	Vd_{ss}	Clearances		
	Rapid	Slow				Total body	Intercompartmental	
							Rapid	Slow
yr	*min*	*min*	*min*	*l*	*l*	*ml/min*	*ml/min*	*ml/min*
20[a]	0.9	28.7	418	8.6	269	639	4495	985
23	0.5	10.5	240	4.6	157	527	3490	2241
33	1.8	39.9	650	18.8	454	597	4234	1599
33	1.1	31.6	611	18.5	381	544	7548	1346
34[a]	0.5	21.1	464	8.1	256	443	7616	1655
34	1.1	23.6	844	22.8	578	495	6806	6302
39[a]	0.6	7.3	328	12.6	250	594	7512	3450
51	1.1	12.1	302	7.2	210	604	1833	1897
56	1.8	50.6	624	14.4	421	606	3321	1239
57	1.3	30.3	542	6.7	244	403	1932	990
64	3.6	36.2	781	18.7	433	533	1451	1090
67	1.7	11.6	561	13.5	349	509	1875	2375
77	0.7	17.0	514	9.4	625	1270	4713	2141
85[a]	3.9	26.4	461	20.8	240	572	1471	718
88	1.3	19.7	658	6.6	225	278	1771	1258
Mean	1.0[b]	18.5[b]	475[b]	12.7	339	574	4005	1952
S.D.	0.6	11.9	193	5.9	139	214	2372	1393

[a] Patient not in table 1.
[b] Harmonic mean.

TABLE 4
Alfentanil pharmacokinetic parameters

Age	Distribution Half-Lives		Elimination Half-Life	V_1	Vd_{ss}	Clearances		
	Rapid	Slow				Total body	Intercompartmental	
							Rapid	Slow
yr	*min*	*min*	*min*	*l*	*l*	*ml/min*	*ml/min*	*ml/min*
20	0.8	17	83	1.84	98.2	166	947	54
23	0.9	14	105	2.89	40.1	449	1187	358
23	0.9	31	101	3.16	12.1	178	1488	25
28[a]	2.2	32	107	4.81	24.5	351	846	66
29	0.5	19	121	1.31	16.3	107	1421	137
32	0.5	20	144	1.27	16.0	120	1213	97
33	0.6	12	118	1.81	22.6	185	1257	244
51	0.8	13	166	2.44	16.9	76	1471	225
51	0.5	8	83	2.15	26.9	327	1665	407
61	0.4	8	124	2.01	26.8	191	2279	422
66	0.7	14	144	1.64	25.4	158	1011	280
69	0.4	9	84	1.53	17.8	204	1517	165
73	1.1	12	121	2.64	35.2	362	780	304
74	0.7	14	223	2.31	28.2	109	1375	252
77	0.9	22	104	1.61	16.4	172	842	103
77	1.2	10	148	2.16	16.3	85	600	358
89	0.5	18	206	1.58	21.7	80	1625	219
Mean	0.67[b]	14[b]	118[b]	2.19	21.9	195	1266	224
S.D.	0.26	5	32	0.86	8.0	111	412	126

[a] Patient not in table 2.
[b] Harmonic mean.

tions at steady state *vs.* age were 0.09 (fentanyl) and 0.16 (alfentanil). Clearances *vs.* age were 0.11 (fentanyl) and −0.30 (alfentanil). The fast intercompartmental clearance for fentanyl decreased with age ($r = -0.62$), but this was not seen for alfentanil ($r = 0.01$). Terminal elimination half-life *vs.* age was 0.24 for fentanyl. Terminal elimination half-life *vs.* age for alfentanil was significant at the $P < .05$ level, with a correlation coefficient of 0.50.

Discussion

Fentanyl *vs.* alfentanil: dose requirement, pharmacodynamics and pharmacokinetics for all patients. The alfentanil/fentanyl dose ratio necessary to produce the same EEG endpoint is 5.44:1. This ratio is consistent with previous reports on the relative potencies of alfentanil and fentanyl derived from experimental and clinical data (Brown *et al.*, 1980, Stanski and Hug, 1982). Although the i.v. bolus dose potency of alfentanil to fentanyl is approximately 5:1, the steady-state serum concentration potency based on the IC_{50} values is approximately 61:1. This difference can be explained by the smaller initial distribution volume and more rapid blood-brain equilibration of alfentanil (Scott *et al.*, 1985). The bolus dose potency and pharmacodynamic parameters found for fentanyl and alfentanil in this study are similar to our previously re-

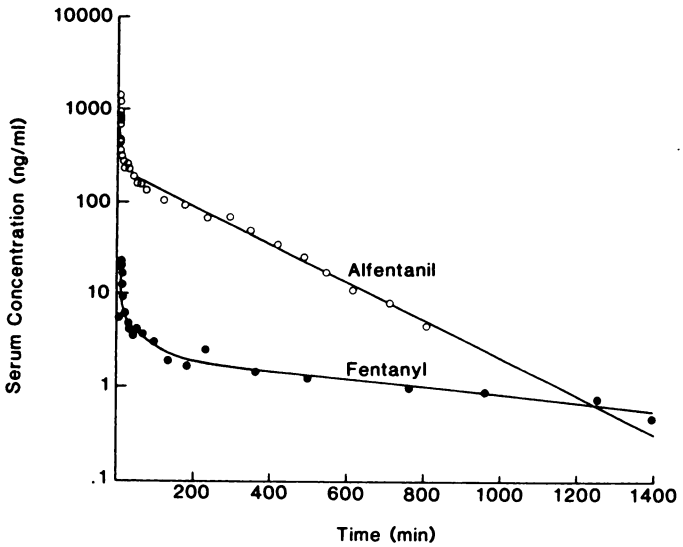

Fig. 4. Fentanyl and alfentanil serum concentrations *vs.* time. Representative curves are shown. Circles (○, alfentanil; ●, fentanyl) are measured concentrations and the solid lines the predicted concentrations. Sampling for alfentanil stopped at 12 hr. Alfentanil has a shorter elimination half-life.

ported values from a smaller group of patients with a narrow age range (Scott *et al.*, 1985).

The fentanyl pharmacokinetic parameters we report differ from previously reported values. Of the many studies on fentanyl pharmacokinetics in the literature (Mather, 1983), there are three studies that appear to be relatively consistent (McClain and Hug, 1980; Bentley *et al.*, 1981; Koska *et al.*, 1981). These studies reported initial and steady-state distribution half-lives similar to our data. The total body clearance in our study (574 ml/min) is approximately two-thirds the value found in the previous reports (McClain and Hug, 1980, 960 ml/min; Bentley *et al.*, 1981, 991 ml/min; Koska *et al.*, 1981, 830 ml/min). Because of this clearance difference, our terminal elimination half-life of 475 min is longer than the other reported values (McClain and Hug, 1980, 219 min; Bentley *et al.*, 1981, 265 min; Koska *et al.*, 1981, 198 min).

These discrepancies may be methodological in origin. McClain and Hug (1980) measured tritiated fentanyl concentrations in volunteers given no other anesthetic drugs. Bentley *et al.* (1981) used gas chromatography to measure fentanyl concentrations in patients given general anesthesia. Koska *et al.* (1981) measured fentanyl concentrations using a radioimmunoassay in surgical patients given general anesthesia.

A major methodological difference between our study and the other studies is the duration of blood sampling. These other studies measured fentanyl concentrations for 8 hr or less. We sampled for 24 hr and, in a large fraction of patients, were able to detect fentanyl for at least 12 hr. A longer duration of sampling may translate into a greater area under the serum concentration *vs.* time curve and thus a lower clearance value and longer terminal elimination half-life. It is possible that the other studies underestimated the true terminal elimination half-life of fentanyl. Recently, Hudson *et al.* (1986) reported fentanyl pharmacokinetics after large doses and 24-hr sampling. Their clearances and volumes of distribution approximate ours.

Our relatively low value for total body clearance could be the result of decreased hepatic blood flow during some portion of our study, attributable to enflurane anesthesia and surgery in our patients (Lehmann *et al.*, 1982b; Mather *et al.*, 1982). However, the patients in the Bentley *et al.* (1981) and Koska *et al.* (1981) studies also had anesthesia and surgery similar to our patients.

As a recent publication by Reilly *et al.* (1984) points out, the pharmacokinetic parameters available in the literature show major discrepancies. Whether these are purely methodological or whether they reflect intrinsic large interpatient variability is unknown.

In a similar fashion, our alfentanil pharmacokinetic parameters differ from previous reported values. Bovill *et al.* (1982) and Camu *et al.* (1982) report initial distribution volumes of 8.7 and 12.3 liters, with steady-state distribution volumes of 57 and 36 liters. These values are somewhat larger than our initial and steady-state distribution volumes. Again, a major difference is seen in the clearance values reported by Bovill *et al.* (1982) (560 ml/min) and Camu *et al.* (1982) (460 ml/min). Our alfentanil clearance value is less than half these values. Our terminal elimination half-life is therefore approximately one-third longer than the values from these other studies. Bovill *et al.* (1982) assayed their alfentanil concentrations using a radioimmunoassay, whereas Camu *et al.* (1982) used gas chromatography. Both studies sampled for only 6 hr. We sampled for 12 hr and were able to detect alfentanil in almost all patients for 8 hr or more. As in our study, their patients had undergone anesthesia and surgery during the study period.

There are no data available to assess whether age-dependent changes in fentanyl or alfentanil disposition or metabolism occur. It is possible that kinetic changes occurred differentially in our patients due to age-related differences in narcotic me-

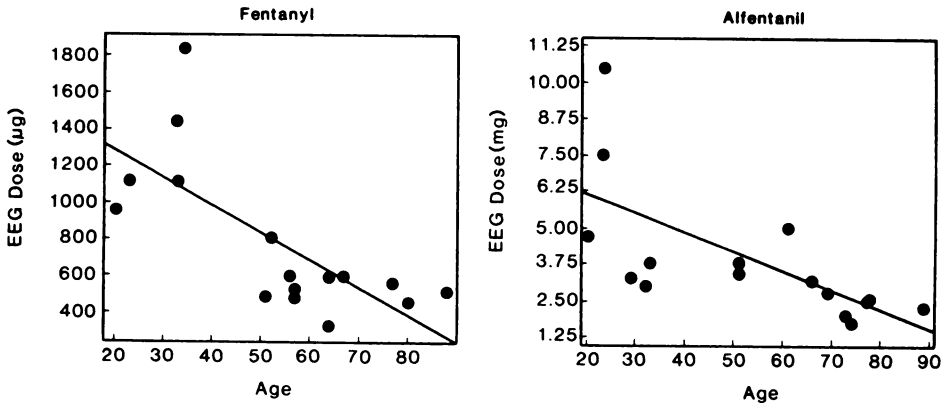

Fig. 5. EEG dose vs. age for fentanyl and alfentanil. The dose administered when δ waves appear in the raw EEG (EEG dose) is plotted against the patient's age. The regression line is shown and has the following equation. Fentanyl: EEG dose = −14.76 × age + 1560. $P < .01$, $r = -0.72$. Alfentanil: EEG dose = −65.7 × age + 7381. $P < .05$, $r = -0.67$.

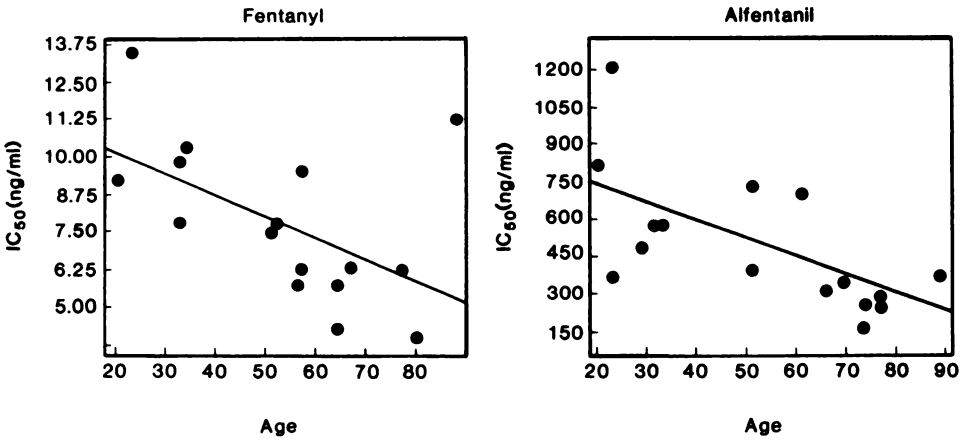

Fig. 6. IC_{50} *vs.* age for fentanyl and alfentanil. The brain sensitivity (IC_{50}) is plotted against the patient's age. The regression line is shown and has the following equation. Fentanyl: $IC_{50} = -0.0675 \times age + 11.4$. $P < .01$, $r = -0.52$. Alfentanil: $IC_{50} = -7.69 \times age + 886$. $P < .01$, $r = -0.66$.

tabolism. We did not discover age-related pharmacokinetic changes, so the impact of this issue is probably small.

Age and fentanyl-alfentanil dose requirements and pharmacokinetics. The results of this study confirm previous clinical impressions of lower narcotic dose requirements with increasing age. Both narcotics had significant negative correlations of age and the dose required to induce EEG δ waves. In contrast to a previous report by Bentley *et al.* (1982), our major fentanyl pharmacokinetic parameters did not correlate with age. Bentley reported a fentanyl terminal elimination half-life of 945 ± 64 min in four elderly females. Blood sampling duration was only 420 min. Therefore, their 945-min terminal elimination half-life and subsequent pharmacokinetic data are unreliable estimates. No other investigators have reported age-related changes in the pharmacokinetics of fentanyl. The finding of an age-related decrease in fast intercompartmental clearance is a possible explanation for the age-related decrease in dose requirement; however, the magnitude of this decrease is small. We found no decrease in the fast intercompartmental clearance rate with age for alfentanil, yet a decreased dose requirement was demonstrated.

The effects of age on alfentanil pharmacokinetics are similar to the effects reported by Helmers *et al.* (1984). They found that the terminal elimination half-life increased from 79 min in young adults to 128 min in the elderly. We, too, found that terminal elimination half-life for alfentanil increased significantly with increasing age. Although Helmers *et al.* (1984) also found that total body clearance of alfentanil decreased in elderly subjects (428 ml/min in the young *vs.* 331 ml/min in the elderly), we did not find clearance significantly affected by age. Perhaps our small group size prevented us from finding a decreased clearance with age.

Age and fentanyl-alfentanil pharmacodynamics. We found that elderly patients have an increased brain sensitivity to fentanyl or alfentanil demonstrated by EEG changes. Although there are reports of decreased narcotic requirements in the elderly (Belleville *et al.*, 1971; Kaiko, 1980; Berkowitz *et al.*, 1975; Owen *et al.*, 1983; Bentley *et al.*, 1982; Helmers *et al.*, 1984; Arunasalam *et al.*, 1983), these studies have not carefully separated pharmacokinetic from pharmacodynamic phenomena. Our study design enabled us to examine in each patient the separate pharmacokinetic and pharmacodynamic components of the individual's dose requirement.

The relationship of narcotic-induced EEG slowing to other more commonly used measures of narcotic effect (analgesia, ventilatory depression and adequate anesthesia when combined with nitrous oxide) has not been established. The range of fentanyl and alfentanil serum concentrations that cause EEG slowing is well within the therapeutic range of these two narcotics. For fentanyl, serum concentrations of approximately 3 ng/ml initiate EEG slowing; one-half the maximal slowing occurs at 7.8 ng/ml; and maximal slowing occurs at approximately 10 ng/ml. Analgesia for mild-to-moderate pain is achieved with concentrations of 2 to 4 ng/ml (Lehmann *et al.*, 1982a; Andrews *et al.*, 1983). Significant respiratory depression occurs at 1.5 to 5 ng/ml (Andrews *et al.*, 1983; Cartwright *et al.*, 1983). When combined with N_2O, adequate anesthetic conditions are obtained with concentrations of 5 to 10 ng/ml; when used alone, narcotic concentrations above 20 ng/ml appear to be necessary (Sprigge *et al.*, 1982).

For alfentanil, EEG slowing starts at approximately 200 ng/ml; half-maximal slowing occurs at 497 ng/ml; and maximal slowing occurs at concentrations around 600 ng/ml. These serum concentrations are also within clinically achieved therapeutic concentrations. O'Connor *et al.* (1983) report ventilatory depression and adequate postoperative analgesia associated with plasma concentrations of 108 ng/ml. Ausems and Hug (1983) have shown that concentrations of 200 to 500 ng/ml combined with N_2O are necessary for adequate anesthesia in patients undergoing intra-abdominal surgery. For cardiac surgery using alfentanil as the primary anesthetic agent, concentrations between 800 and 1500 ng/ml appear to be necessary to control hemodynamic responses (deLange and de Bruijn, 1983).

The reasons for altered brain sensitivity to narcotics with aging could not be determined from this study. The lower IC_{50} values in older patients suggest that narcotics will have a greater effect than in younger patients at the same steady-state serum concentration.

Age-related changes in fentanyl or alfentanil serum protein binding have not been reported. Unpublished preliminary protein-binding studies in our laboratory show no significant differences in protein binding with age, but we did not perform binding studies on the patients in this study.

Possible explanations for increased sensitivity in older patients may involve changes in the number of opiate receptors, aging-related changes in opiate receptor binding or increased translation of binding into effect. Although no human data exist for these types of studies, some experimental evidence is available.

Several investigators (Agnati *et al.*, 1984; Messing *et al.*, 1980) have shown decreases in the number of opiate receptors (both

mu and *delta*) in older rats. Hess *et al.* (1981) found that no aging-related changes in opiate binding affinities occurred in rats. How these findings translate into explanations for humans is not clear.

The implications of this study are that older patients are more "sensitive" to narcotics for pharmacodynamic reasons. Consequently, drug regimens for elderly patients should be designed to achieve lower serum concentrations and to avoid an accumulation of drug in body tissues that might lead to prolonged high serum concentrations. More research is necessary to identify the reasons for increased sensitivity in the elderly and should focus on age-related changes at the receptor level rather than seeking explanations for differences in age-related changes in drug distribution.

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