

Increased Sensitivity to Etomidate in the Elderly: Initial Distribution versus Altered Brain Response

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To determine the effect of aging on the pharmacokinetics and pharmacodynamics of etomidate, we administered etomidate (5 to 10 mg/min) by intravenous infusion to 21 healthy surgical patients, age 22 to 82 yr. Etomidate produced progressive slowing of the EEG to an easily recognized pattern (stage 3) that determined the dosage endpoint. Subsequent power-spectrum analysis of the EEG gave the median frequency. Median frequency values and simultaneous measurements of blood etomidate concentration were incorporated into a sigmoid E_{\max} pharmacodynamic model that permitted an estimate of IC_{50} , the blood etomidate concentration which produced a 50% reduction in the median frequency. The dose of etomidate required to reach the uniform EEG endpoint decreased significantly with increasing age ($r^2 = .68$) as did the dose needed to produce maximal median frequency depression ($r^2 = .69$). None of the parameters of the pharmacodynamic effect model, including IC_{50} , correlated with age, suggesting that increased brain sensitivity in the elderly does not cause the age-related change in dose requirement. The initial distribution volume for etomidate decreased significantly with increasing age ($r = .56$), implying that a higher initial blood concentration in the elderly following any given dose of etomidate is part of the cause of the lower dose requirement in the elderly patient. A contracted initial distribution volume in the elderly may result from well described physiologic changes of age. Etomidate clearance also decreased with age. Age-dependent changes in etomidate pharmacokinetics rather than altered brain responsiveness may be the basis for the decreased etomidate dose requirement in the elderly. (Key words: Anesthetics, intravenous: etomidate. Brain: electroencephalography. Pharmacokinetics: distribution; kinetics. Potency, anesthetic: age factors.)

CLINICAL OBSERVATIONS INDICATE that older patients are more sensitive to most anesthetic agents. MAC decreases with increasing age¹ as does the dose requirement for barbiturates.² A pharmacokinetic explanation of the age-dependent, dose-response relationship for thiopental was recently proposed by Homer and Stanski.³ The lower dose requirement in older patients resulted from a smaller

initial distribution volume. No alteration in brain sensitivity to thiopental concentration (pharmacodynamics) could be demonstrated.

Etomidate is an intravenous hypnotic agent used for the induction and maintenance of anesthesia. It is an imidazole and, thus, differs chemically from the thiobarbiturates. Hemodynamic stability is one of etomidate's major advantages,⁴ making it an agent of considerable usefulness in elderly patients or patients with compromised circulatory reserve. The age-dose relationship for etomidate is not known.

In the present study, we examined the age-dose relationship for etomidate and analyzed the contributions of pharmacokinetics and pharmacodynamics to that relationship. Because the chemical structure of etomidate differs from that of thiopental, we believe that the finding of a consistent explanation for the dose-response relationship for both drugs in elderly patients would suggest a general principle applicable to altered dose-response relationships for intravenous anesthetics in the elderly.

Methods

PATIENT POPULATION

After institutional review board approval, informed consent was obtained from 21 ASA I-II patients (20 men, one woman), ages 22 to 82 yr (weight, 81.9 ± 11.5 kg), scheduled for elective surgery. All patients were free of significant cardiovascular, renal, or hepatic disease by routine preoperative screening. We excluded patients who abused drugs or alcohol. Blood sampling was incomplete in one patient, and data from this patient were used for pharmacodynamic analysis only. Pharmacokinetic data only were collected for four patients. Thus, pharmacokinetic data are given for 20 patients and pharmacodynamic data are given for 16 patients.

Following premedication with glycopyrrolate 0.2 mg im, patients were brought to the operating room. Standard intraoperative monitors were applied, and a radial arterial catheter was inserted. Bilateral frontal and temporal EEG leads were recorded. We later selected the channel with the least artifact for further EEG analysis. Patients breathed 100% oxygen by mask during the study. After a 3-min baseline recording, etomidate was administered intravenously at a constant rate of 5 to 10 mg/min by infusion pump until a previously reported EEG pattern of stage 3 anesthesia was attained,⁵ at which point

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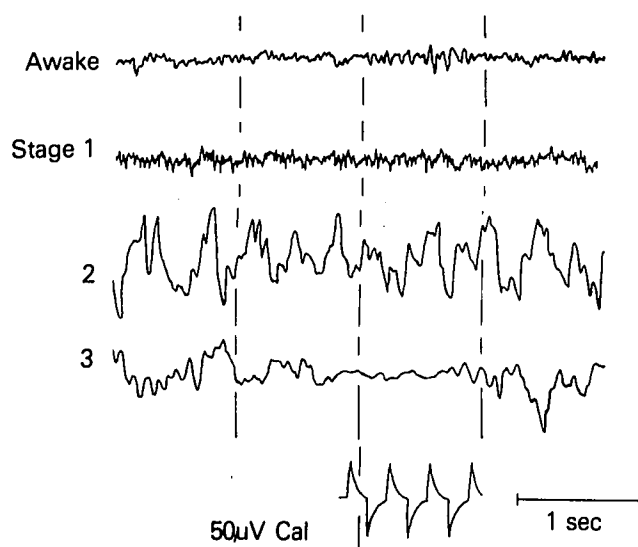


FIG. 1. The EEG progression with increasing concentration of etomidate. In stage 1, a small increase in both amplitude and frequency was observed. Patients became drowsy during this stage. Stage 2 consisted of higher amplitude, lower frequency waves. This progressed to stage 3 where high-amplitude, slow waves were interspersed with 1- to 2-s periods of high-frequency, low-amplitude waves. This pattern is similar to burst suppression seen with thiopental.

we stopped the infusion. Patients were then allowed to recover (approximately 20 min) until signs of responsiveness or a stage 1 EEG pattern was observed. Myoclonus, which is sometimes seen with etomidate,^{6,7} produced EEG artifacts, and transient relaxation with succinylcholine and controlled ventilation were required to circumvent this problem. Increases in heart rate above 120/min were controlled with propranolol. Nitroprusside was given when mean arterial pressure exceeded 125 mmHg. Arterial blood gases were measured at the peak of etomidate's effect to confirm that ventilation was adequate.

Arterial blood samples for whole blood etomidate concentration were collected in heparinized plastic tubes at 0.5-min intervals during infusion and at 1- to 3-min intervals during recovery. Arterial blood samples were obtained for pharmacokinetic analysis at 20, 25, 30, 45, 60, 90, and 120 min after the beginning of the infusion. Venous blood samples were collected at 3, 4, 5, 6, 8, 10, and 12 h. Following recovery, patients were reanesthetized with thiopental 3 to 4 mg/kg and were given succinylcholine for tracheal intubation. Anesthesia was maintained with 70% N₂O in oxygen and enflurane 1% to 2% with morphine or meperidine supplementation and pancuronium for muscle relaxation, if needed.

Heparinized blood samples were frozen at -12° C until they were analyzed. Whole blood etomidate concentration was determined by high-pressure liquid chromatographic assay⁸ sensitive to 2 ng/ml with a coefficient of variation of 5.4% at 5 ng/ml.

EEG DATA ANALYSIS

The progression of EEG changes with increasing concentrations of etomidate is depicted in figure 1. These stages, analogous to those described for thiopental, have been previously reported by Meinck.⁹

The EEG was recorded on FM magnetic tape (Vetters® Model A Recorder) for off-line analysis. The amplified signal was divided into 2.56 s epochs, digitized, and transformed by fast Fourier analysis using a PDP® 11/23 computer (Digital Equipment Corp., Lexington, MA). These consecutive epochs were converted to a series of power (amplitude squared) *versus* frequency histograms.¹⁰⁻¹² The continuum of histograms thus describes the analog EEG waveform. The waveform information of the histograms was further condensed by describing each histogram in terms of the median frequency, *i.e.*, the frequency below which 50% of the area under the power-frequency histogram is located. We also determined the spectral edge, *i.e.*, the frequency below which 95% of the power is found. Each epoch of the original complex EEG signal is thus described as a single, representative median frequency or spectral edge value. Curve smoothing is performed to reduce noise. This technique substitutes for each epoch the mean of the epoch itself plus five epochs that precede it and five epochs that follow it. Smoothing, therefore, produced a "moving mean" of 11 epochs of the median frequency or spectral edge.

PHARMACODYNAMIC DATA ANALYSIS

The relationship between etomidate concentration and the change in median frequency is described by an inhibitory E_{\max} pharmacodynamic model^{13,14}:

$$E = E_0 - \frac{E_{\max} \cdot Ce^{\gamma}}{IC_{50}^{\gamma} + Ce^{\gamma}} \quad (1)$$

where E is the median frequency at a given time in Hz; E_0 is the baseline median frequency (Hz); E_{\max} is the maximum slowing of the median frequency; IC_{50} is the blood etomidate concentration in ng/ml that produces 50% of the maximal median frequency depression; γ is a dimensionless term describing the slope of the sigmoid concentration *versus* effect curve; and Ce denotes the concentration of the drug at the effect site in the brain, a drug level that cannot yet be measured but that is conceptualized as the concentration in a hypothetical pharmacokinetic "effect compartment." This compartment has a rate constant (k_{eo}) and half-time ($T_{1/2k_{eo}}$) for equilibration with the initial distribution volume. The value of $T_{1/2k_{eo}}$ reflects the rapidity of onset of the drug effect independent of its changing blood level. $T_{1/2k_{eo}}$ includes processes at the macromolecular level such as perfusion, diffusion, tissue solubility, and drug receptor interactions that occur after

a blood level is reached but before an effect is observed. Values of the pharmacodynamic parameters were determined by nonlinear regression. The BMDP statistical package (1983) was used to describe the data and to perform linear regression analysis of the data and of the derived pharmacodynamic parameters. A value of $P < 0.05$ was considered statistically significant.

DOSE REQUIREMENT DETERMINATION

EEG records were analyzed retrospectively by a blinded observer trained in EEG pattern recognition. The dose requirement was defined as the amount of etomidate infused at the time that the stage 3 EEG was first noted by the interpreter. The minimum median frequency is defined as the earliest frequency recorded whose value was within 10% of the lowest median frequency recorded. Minimum spectral edge was similarly defined. The dose required to reach minimum median frequency or spectral edge was the amount of drug infused when these frequency values were attained.

PHARMACOKINETIC DATA ANALYSIS

Whole blood etomidate concentration *versus* time data were fit by open two- and three-compartment mammillary models using extended least squares nonlinear regression.[§] The statistically preferred model was selected in each case using log likelihood values. Standard pharmacokinetic formulas were used to calculate clearance, distribution rate constants, and half-lives. Pharmacokinetic data and parameters were analyzed as described for pharmacodynamic data with a significance level of $P < 0.05$.

Results

DOSE REQUIREMENT

The EEG gradually slowed during infusion of etomidate (fig. 1). The progression was similar to that seen during infusion of thiopental except that no isoelectric intervals between high amplitude, slow waves (burst suppression) were seen with etomidate even at a dose of 1 mg/kg. The stage 3 EEG endpoint was easily recognized and used as the endpoint for infusion.

The etomidate dose required to reach the stage 3 endpoint decreased significantly with increasing age ($r^2 = .68$; fig. 2). This dose showed a 5.4-fold range from 0.134 mg/kg in an 80-yr-old patient to 0.725 mg/kg in a 22-yr-old patient. The calculated dose to reach maximal me-

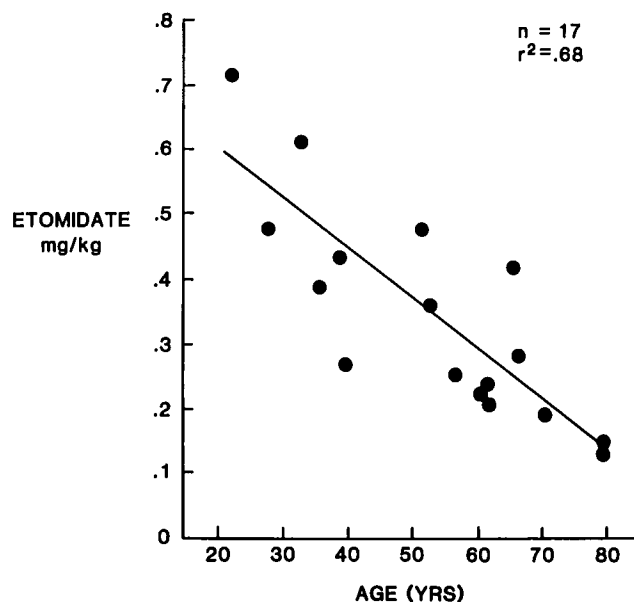


FIG. 2. Etomidate dose required to reach the EEG stage 3 endpoint decreased with increasing age. Because etomidate was administered by rapid infusion, doses shown are slightly higher than the bolus dose required for an equivalent effect.

dian frequency slowing also decreased significantly with increasing age ($r^2 = .69$). The dose to reach maximal median frequency slowing correlated well ($r^2 = .80$) with the dose to EEG stage 3. Although the dose to maximal spectral edge slowing correlated with age ($r^2 = .38$) and with the dose to EEG stage 3 ($r^2 = .36$), the correlations were weaker than for median frequency. Neither age nor etomidate dose requirement correlated with patient weight.

PHARMACODYNAMICS

The EEG was recorded and analyzed in 16 patients. The relationship of median frequency to etomidate concentration during a 25-min period is shown for one patient (fig. 3). During infusion of etomidate, the EEG gradually slowed, with median frequency reaching its lowest value shortly after peak blood concentrations were reached. Median frequency then returned to baseline values as blood etomidate concentrations declined. The close parallel relationship between etomidate blood levels and median frequency was seen for all 16 patients.

The $T_{1/2}k_{eo}$ between blood and the hypothetical effect site in the brain was not age dependent ($1.6 \pm .5$ min, table 1), nor was IC_{50} (388 ± 144 ng/ml). Values of γ , the power function, were unrelated to age.

PHARMACOKINETICS

Complete pharmacokinetic analysis was performed for 20 patients. In two cases, simultaneous arterial and venous

§ Sheiner LB: ELSFIT—A Program for the Extended Least Squares Fit to Individual Pharmacokinetic Data. Technical Report, Division of Clinical Pharmacology, University of California, San Francisco, California, Feb, 1981.

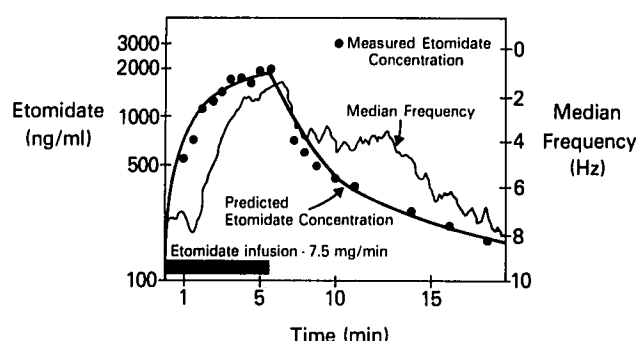


FIG. 3. Relationship of blood etomidate concentration to EEG median frequency change for a 53-yr-old patient. Etomidate was given until the stage 3 EEG endpoint was noted and then stopped to allow clinical or EEG recovery. Note that the axis of the median frequency plot is inverted for visual clarity and that median frequency tracks the changing blood concentration. Similar data were obtained for all 16 patients.

samples were obtained for the entire study period. In all cases, a three-compartment pharmacokinetic model was statistically preferred to a two-compartment model. Pharmacokinetic data are summarized in table 2.

Figure 4 shows the initial 25 min of etomidate blood concentration data for a young (22-yr-old) and an elderly (67-yr-old) patient. Both patients received etomidate at the same rate (7.5 mg/min) and achieved similar blood concentrations of etomidate (≈ 2000 ng/ml) at the EEG endpoint. The elderly patient required approximately one-half as long to reach this endpoint (3.5 min) as the young patient (6.6 min).

The initial distribution volume for etomidate decreased significantly with increasing age ($r = .56$, fig. 5). Calculated

from the data for the youngest and oldest patients, the initial distribution volume decreased by 42%.

No age-related changes were shown in steady-state volume of distribution or in the volumes of the peripheral compartments (table 2). The mean steady-state volume of distribution was 4.7 ± 1.8 l/kg.

Clearance of etomidate decreased significantly with age ($r^2 = .28$), declining approximately $2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for every decade in the age range studied. No age-related change could be demonstrated for distribution or elimination half-lives, intercompartmental clearances, or rate constants. Because total blood etomidate was measured, red blood cell to plasma ratios for etomidate were not examined. Protein binding was not measured.

To calculate plasma clearance, blood etomidate concentration was related to plasma concentration by:

$$C_{bl} = (C_{pl} \times F_{pl}) + \left(C_{rbc} \times \frac{\text{Hct}}{100} \right)$$

where C_{bl} and C_{pl} are the blood and plasma etomidate concentrations, respectively; F_{pl} is the plasma fraction of the blood; C_{rbc} is the etomidate concentration in the red blood cell; and Hct is the hematocrit. Because plasma to red blood cell partitioning of etomidate is approximately equal to 1.30,¹⁵ etomidate blood concentration values were converted to plasma values by:

$$C_{pl} = \frac{C_{bl} \times 130}{130 - .30 \text{ Hct}}$$

Plasma clearances were calculated from these concentration values and are shown in table 2.

TABLE 1. Etomidate Pharmacodynamic Data (n = 17)

Age (yr)	Dose (mg/kg)	$T_{1/2K_{e0}}$ (min)	IC_{50} (ng/ml)	E_0 (Hz)	E_{max} (Hz)	γ (—)
80	0.13	2.4	212	8.0	5.2	9.5
80	0.15	2.1	442	8.3	6.1	4.1
71*	0.19	—	—	—	—	—
67	0.29	1.2	354	8.2	6.2	2.5
66	0.42	1.0	782	9.1	8.4	1.8
62	0.22	1.4	417	8.8	7.3	2.6
62	0.24	2.4	199	10.1	8.3	1.4
61	0.23	0.9	348	7.7	5.1	5.8
57	0.25	2.2	275	9.7	7.7	6.7
53	0.36	2.1	453	8.6	5.6	3.9
52	0.48	1.4	373	10.3	8.2	3.3
40	0.26	1.9	348	8.9	7.6	2.4
39	0.43	1.2	587	8.4	6.3	3.6
36	0.39	1.1	283	10.5	9.0	1.6
33	0.61	1.4	452	9.5	7.2	4.6
28	0.48	1.1	392	10.6	8.1	2.2
22	0.73	1.9	288	10.3	8.0	4.2
Mean 53.5	0.35	1.6	388	9.2	7.2	3.8
SD 17.7	0.17	0.5	144	0.96	1.2	2.1

See "Methods" for abbreviations.

* EEG monitored only.

TABLE 2. Etomidate Pharmacokinetic Data (n = 20)

Age (yr)	Total Dose (mg/kg)	Initial Distribution Volume (l/kg)	V _{d_{ss}} (l/kg)	Clearance (whole blood) (mg · kg ⁻¹ · min ⁻¹)	Calculated Plasma Clearance (mg · kg ⁻¹ · min ⁻¹)	Rapid Inter-compartmental Clearance (ml · kg ⁻¹ · min ⁻¹)	Slow Inter-compartmental Clearance (ml · kg ⁻¹ · min ⁻¹)	Rapid Distribution Half-life (min)	Slow Distribution Half-life (min)	Terminal Elimination Half-life (min)
82	0.48	0.072	2.9	28.2	26.0	51.6	22.6	0.45	6.5	147
80	0.37	0.048	6.8	13.6	12.5	15.0	9.3	0.85	8.8	648
80	0.29	0.046	2.9	12.5	11.4	9.5	7.9	1.0	10.8	361
71	0.33	0.074	3.9	15.4	14.0	31.6	21.0	0.72	13.6	284
71	0.37	0.063	3.9	24.2	22.0	34.0	29.5	0.47	6.3	194
70	0.40	0.073	3.2	13.4	12.0	18.6	18.1	0.95	10.1	270
67	0.31	0.108	8.9	12.1	10.9	26.6	19.1	1.2	26.4	797
66	0.48	0.118	5.5	15.8	14.4	25.6	23.1	1.2	13.8	387
62	0.37	0.095	7.3	18.3	16.5	30.5	16.2	0.97	9.1	433
62	0.31	0.076	5.4	13.2	11.9	21.9	17.6	0.95	12.9	441
61	0.36	0.053	3.0	16.3	14.6	17.8	16.4	0.71	13.4	240
57	0.32	0.132	7.2	34.1	31.5	26.4	25.5	1.0	15.3	318
53	0.46	0.077	3.2	15.5	13.8	21.7	18.9	0.88	8.5	245
52	0.76	0.123	4.2	22.7	20.9	25.7	18.2	1.2	19.5	259
40	0.53	0.099	4.0	24.4	21.7	29.5	20.9	0.85	8.5	235
39	0.60	0.124	5.0	24.8	22.1	29.2	18.4	1.1	19.5	294
36	0.43	0.104	5.9	22.2	19.7	28.1	19.1	1.0	13.4	314
34	0.71	0.123	4.8	21.1	18.9	23.2	16.8	1.3	9.4	289
28	0.67	0.091	3.1	26.3	23.5	20.6	20.1	0.89	9.2	178
22	0.99	0.094	2.8	31.7	28.4	22.7	17.2	0.87	7.4	138
Mean 56.7	0.48	0.090	4.7	20.3	18.3	25.5	18.8	0.93	12.1	324
SD 18.0	0.19	0.027	1.8	6.6	6.1	8.6	4.8	0.23	5.1	162

V_{d_{ss}} = volume of distribution of steady state.

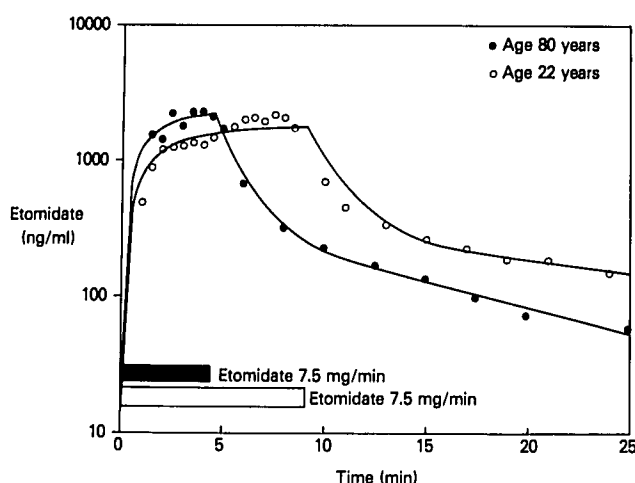


FIG. 4. Etomidate concentration *versus* time during the infusion and recovery phases for two patients at the extremes of age. The younger patient required almost twice the dose of etomidate to reach similar blood concentrations.

In two patients, simultaneous arterial and venous data were compared between 3 and 12 h following infusion. Arterial blood etomidate concentrations were consistently less than corresponding venous blood levels. However, calculated values of clearance and elimination half-life based on each type of sampling differed by less than 12%.

During etomidate infusion or in the subsequent recovery period, 12 of 21 patients had transient increases in mean arterial pressure (MAP) and received nitroprusside to keep MAP less than 130 mmHg. Seven of these 12

patients also developed sinus tachycardia and received incremental doses of propranolol (0.5 mg iv, maximum dose 2 mg) intravenously to maintain heart rate below 120/min. The incidence of hypertension or tachycardia was not related to age.

Arterial blood gases during this study showed a mean P_{CO_2} of 40 ± 5 mmHg and a normal pH. All patients were well oxygenated throughout the study.

All patients developed myoclonic muscle movement unless neuromuscular blockade was used. The EEG showed no evidence of abnormal activity at any time during the study. Myoclonus was seen both during etomidate infusion and following termination of the infusion. No pattern in the degree of myoclonus or in the muscle groups involved could be determined.

Discussion

The EEG is a continuous, sensitive indicator of etomidate's cerebral effects during the induction of anesthesia. Unlike clinical signs of the depth of anesthesia, such as the lid reflex or the autonomic response to laryngoscopy, the EEG is continuous, noninvasive, and does not perturb its own measurement. While the clinical significance of anesthetic-induced EEG changes has not been precisely determined, Meinck *et al.* reported the absence of EEG signs of arousal following noxious stimuli during stage 3 etomidate anesthesia.⁹ The stage 3 EEG endpoint thus approximates a level of surgical anesthesia.

In keeping with the clinical observation that the elderly are more sensitive to intravenous anesthetics, we found an age-related decrease in the dose of etomidate needed to achieve a uniform stage 3 EEG endpoint. An 80-yr-old patient required less than one-half the dose of etomidate to reach the same endpoint as a 22-yr-old patient. The dose requirement in our study is higher than that following intravenous bolus administration because etomidate was given by intravenous infusion over 3 to 9 min, and drug distribution occurred while the drug was being infused.

We could not demonstrate a pharmacodynamic change with age for etomidate. There was no age-related change in brain sensitivity (IC_{50}) to etomidate (table 1). For comparison with other published values, we used equation 2 to convert our whole blood IC_{50} to a plasma IC_{50} for each patient. Our mean value of plasma IC_{50} (430 ± 160 ng/ml) is higher than the mean plasma value of 307 ng/ml reported by Fragen *et al.*¹⁶ when patients awoke after an etomidate infusion, presumably because patients awaken when EEG slowing is less than half maximal. Using venous sampling, Schüttler *et al.*¹⁷ reported a somewhat lower IC_{50} of 310 ng/ml for EEG median frequency slowing during an etomidate infusion. They also measured a mean etomidate plasma concentration of 310 ng/ml when patients became unresponsive to verbal stimuli.¹⁸

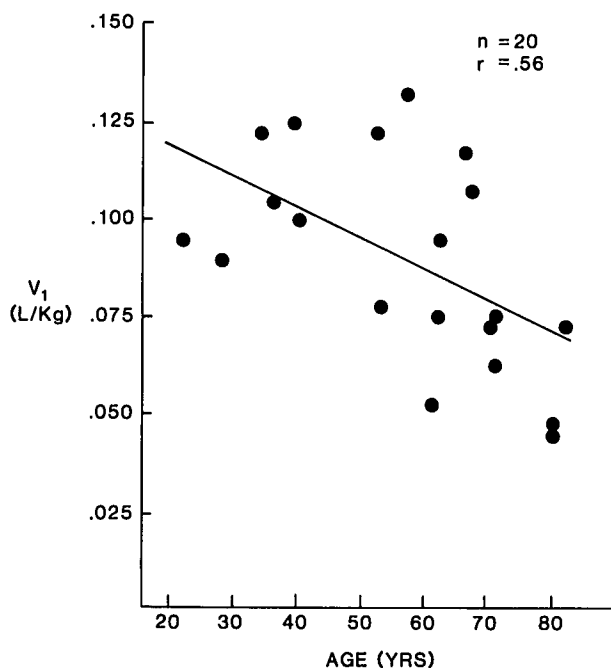


FIG. 5. Relationship of the initial distribution volume for etomidate to age showing a significant negative correlation with age.

The rate of equilibration between blood and the site of etomidate's effect in the brain ($T_{1/2k_{eo}}$) showed no age dependence. The small values of $T_{1/2k_{eo}}$ (0.92–2.4 min) reflect the rapid movement of etomidate from blood to brain and are similar to those for thiopental (0.6–2.5 min).³ The $T_{1/2k_{eo}}$ for nondepolarizing muscle relaxants is 5 to 8 min,¹⁴ which is consistent with their clinically slower onset of action.

There is, however, a pharmacokinetic change with age for etomidate. The present results indicate that the decreased requirement for etomidate in the elderly *versus* the young is, in part, a consequence of a smaller initial distribution volume in the elderly. A given dose of etomidate results in a higher initial blood concentration in the elderly because of this smaller initial distribution volume.

The initial distribution volume of a drug has the dimensions of liters, but it is not truly a physiologic space.¹⁹ Instead, the initial distribution volume equals the amount of drug in the body following injection and instantaneous mixing divided by the initial concentration in the blood. That initial concentration is estimated by the pharmacokinetic curve-fitting process. The initial distribution volume of a drug depends on several factors that affect the drug concentrations measured within the first few min after injection. These include: vascular volume; cardiac output; the distribution of blood flow to the different organs and within each organ; solubility and partitioning in rapidly equilibrating tissues; and protein binding.^{20,21} Several of these determinants of the initial distribution volume are age dependent.^{22,23}

The initial distribution volume for etomidate decreased by 42% between ages of 22 and 80 yr. During this period, cardiac output decreases by 30% to 40%,²⁴ systemic vascular resistance may rise,²² renal blood flow declines by about 35%,²⁵ and hepatic perfusion falls by as much as 40%.²⁵ Cerebral blood flow may decline and renal mass²⁶ may be lost with increasing age. All of these physiologic changes of aging would result in a smaller initial distribution volume and higher blood concentrations in the elderly.

We have shown a negative correlation of initial distribution volume with age for etomidate. While this finding is consistent with the physiology of aging, our data do not permit a more precise description of this relationship that would allow accurate prediction of the initial distribution volume for etomidate based on a patient's age. In view of this, we have included only the correlation coefficient (*r*) for these data.

Homer and Stanski³ found the dose requirement for thiopental decreased by 65% in patients aged between 22 and 88 yr. At the same time, the calculated initial distribution volume decreased by 90%. The larger change in initial distribution volume for thiopental than for etomidate may be attributed in part to the greater degree of

myocardial depression with thiopental²⁷ and a greater sensitivity of the elderly to this effect.

Although the initial distribution volume was age dependent, we found no change in the steady-state volume of distribution. Previous work with fat-soluble drugs like diazepam has shown an increase in the steady-state volume of distribution in the elderly,²⁸ and this has been related to the 20% to 35% increase in body fat content in the elderly.²³ However, the steady-state volume of distribution for other benzodiazepines like oxazepam and lorazepam is unchanged^{29,30} or may even decrease³¹ with age. In addition, etomidate, thiopental, and diazepam all have similar lipid solubility (log *P* between octanol and water = 2.99, 2.93, 2.82, respectively),^{32,†} but only diazepam has an age-related, steady-state volume of distribution.^{3,28} This suggests that lipophilicity is only one determinant of steady-state volume of distribution and that differences in tissue mass, tissue perfusion, and blood–tissue solubility also contribute significantly to its value. While we could demonstrate the impact of age-related physiologic changes on initial distribution volume for etomidate, we could not do this for the steady-state volume of distribution that is governed by more complex processes.

Altered clearance in the elderly has been suggested for both barbiturates³³ and benzodiazepines,³¹ although data are limited and conflicting.^{3,28,30} We found that etomidate's clearance decreased with increasing age. This is consistent with the decline in hepatic blood flow among the elderly because etomidate's clearance depends on hepatic blood flow.³⁴ A decrease in hepatic perfusion during general anesthesia may also have contributed to reduced etomidate clearance.³⁵

Because of the variability in steady-state volume of distribution, elimination half-life was not age related despite the effect of age on clearance. Fast and slow intercompartmental clearances were of similar magnitude and showed no age relation, which implies that age does not measurably alter transfer of etomidate from the initial distribution volume.

Other studies have used the EEG spectral edge to model the CNS effects of thiopental³ and fentanyl.³⁶ We found the median EEG frequency to be a better measure of etomidate's EEG effects. In three patients spectral edge was a sensitive measure of the transition between the awake state and stage 2 anesthesia but was less affected during transitions between deeper anesthetic levels (fig. 6). Spectral edge is more sensitive than median frequency to an EEG power spectrum that is skewed by high frequency (>13 Hz) waves seen with arousal and anxiety. In more anxious patients, the loss of these frequencies during

† Leo A, Hausch C: Partition coefficients and their uses. *Chemical Abstracts* 71:523–616, 1971.

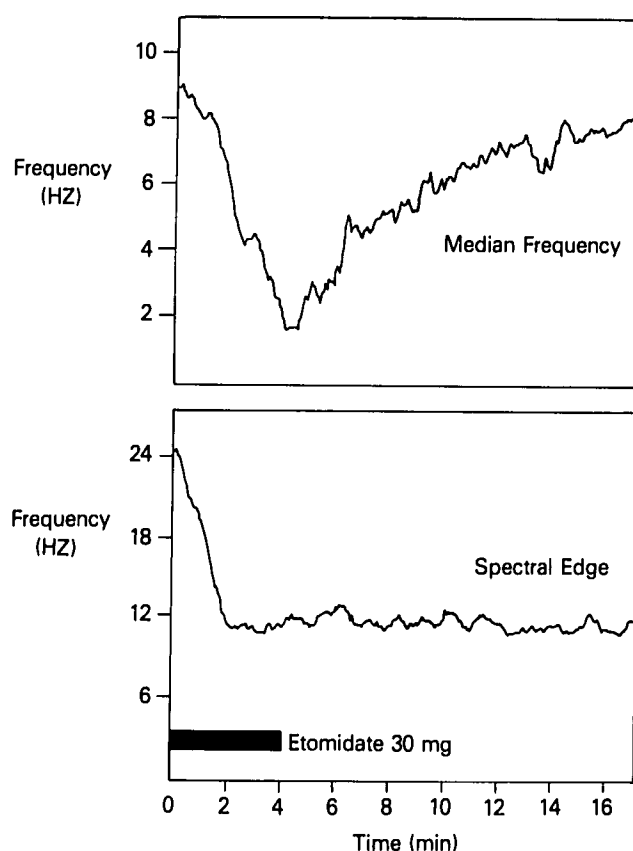


FIG. 6. Simultaneous EEG median frequency and spectral edge plots during the infusion and recovery phases for a 66-yr-old patient. While median frequency change reflected etomidate concentration, spectral edge showed an early decline and plateau without subsequent recovery. A similar discrepancy was observed in two other patients.

the onset of anesthesia can result in a large decline of the spectral edge during light levels of anesthesia. This large decline overshadows subsequent decreases in spectral edge during deepening of anesthesia. The spectral edge may not return toward its awake values until a similar state of arousal is reached. In addition, a moderate amount of high-frequency activity has been reported to persist during generalized slowing of the EEG following ketamine,³⁷ which could also limit the response of spectral edge to EEG changes at deeper levels of anesthesia.

The myoclonic side effects of etomidate were prominent and required suppression with neuromuscular blockade. Studies in animals indicate that etomidate has a disinhibitory effect at the spinal level.³⁸ This explanation is supported by the absence of EEG activation during periods when patients would have demonstrated myoclonus had they not been paralyzed.

We frequently saw hypertension and tachycardia during this study. These hemodynamic responses were not associated with EEG signs of arousal and could have a reflex mechanism similar to that for the motor hyperac-

tivity seen with etomidate. Elevated blood pressure and heart rate are rarely seen clinically because anesthetic levels of etomidate are seldom allowed to rise and decline gradually in the absence of other anesthetic agents, as our study required.

In summary, we demonstrated age dependence in the etomidate dose requirement to produce sleep and a uniform EEG pattern. An age-related pharmacokinetic change, the contraction of the initial distribution volume, is a partial explanation for the dose requirement. The finding that both etomidate and thiopental exert their more pronounced effect in the elderly by a similar alteration of early drug distribution implies that other classes of rapidly acting drugs may be affected by the same mechanism. It may be possible to describe a unifying pharmacokinetic principle that governs the dosage of intravenous anesthetic agents in the elderly.

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