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Pharmacokinetics of Etomidate, a New Intravenous Anesthetic

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Etomidate sulfate, 0.3 mg/kg, was administered intravenously to eight patients and venous blood samples were drawn at intervals for the subsequent 10 hours. Plasma etomidate was determined by mass fragmentography. Plasma concentrations were fitted to a triexponential equation consistent with a three-compartment open pharmacokinetic model. Mean (±SD) variables were: initial $t_{1/2}$, 2.6 ± 1.3 min; intermediate $t_{1/2}$, 28.7 ± 14.0 min; apparent elimination $t_{1/2}$, 4.6 ± 2.6 hours; volume of the central compartment, 23.2 ± 11.4 l; total apparent volume of distribution, 4.5 ± 2.2 l/kg; fraction of drug in the central compartment, 7 per cent; total plasma clearance, 860 ± 230 ml/min. Total blood clearance was estimated to be 754 ml/min and hepatic clearance, 739 ml/min. The large apparent volume of distribution indicates considerable tissue uptake. The hepatic clearance, being about 50 per cent of hepatic blood flow, indicates that changes in hepatic blood flow or hepatic metabolism will have only moderate effects on etomidate disposition. (Key words: Anesthetics, intravenous: etomidate. Pharmacokinetics: distribution; kinetics.)

ETOMIDATE [R-(+)-ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate sulfate] is currently being evaluated for use as an intravenous anesthetic. Animal studies show the drug to be a potent hypnotic with a wider margin of safety than thiopental, methohexital and propanidid.[1] Clinical studies indicate that etomidate produces rapid induction of anesthesia with minimal cardiovascular and respiratory changes.[2,3] We recently developed a sensitive, specific assay for the measurement of etomidate in plasma,[4] which we used in this study to determine the kinetics of the drug in human subjects given a single intravenous dose.

Methods

Subjects for the study were patients who underwent anesthetic induction with etomidate for eye or ear surgery (table 1). All were otherwise healthy, had normal hepatic and renal function, and were taking no other medication. Informed written consent was obtained. Each received diazepam, 10 mg, and scopolamine, 0.3 mg, intramuscularly, 30 min prior to etomidate injection. An indwelling cannula was placed in an antecubital vein for blood sampling. Etomidate, 0.3 mg/kg, as the sulfate in a buffered acidic solution (*p*H 3.0) containing 1.5 mg/ml,§ was then administered intravenously over a 30-sec period into an antecubital vein of the other arm. Anesthesia was maintained with nitrous oxide–oxygen and enflurane, 1–2 per cent, administered from a Copper Kettle vaporizer in a semiclosed circuit. Several patients received a single dose of succinylcholine chloride, 40–60 mg, to facilitate endotracheal intubation. Durations of the operations averaged three and a third hours. Arterial blood-gas values, blood pressure, pulse rate and temperature were maintained in the normal range. Surgical blood loss was less than 100 ml and intravenous fluid administration less than 1,000 ml in every case. The patients were recumbent throughout the period of blood sampling.

Blood samples were withdrawn through the indwelling venous cannula into heparinized glass syringes. Samples were taken just prior to and 4, 8, 15 and 30 min after injection, then hourly to 10 hours. The blood samples were immediately transferred to 15-ml glass-stoppered centrifuge tubes containing heparin and 10 μl of saturated potassium fluoride solution (to inhibit plasma esterase activity). The plasma was separated by centrifugation at 2,000 rpm for 15 min. In rats, etomidate is hydrolyzed in the plasma.[5] Hydrolysis does not occur in human plasma, however, and we have shown that etomidate concentrations in our samples are stable during four hours of incubation at 37 C even in the absence of fluoride (unpublished data). The samples were frozen and stored at −15 C until analyzed.

Plasma concentrations of etomidate were determined by ether extraction and combined gas chromatography–mass spectrometry as previously described.[4] The method is specific for etomidate and sensitive to 1 ng/ml. Each sample was analyzed in duplicate.

Plasma level data were analyzed with the aid of an IBM 360/65 computer, and a program for nonlinear least-squares regression analysis.[6] Data from each individual subject were sequentially fitted to a monoexponential and then to successive polyexponential equations of the general form

$$C_p(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} \ldots\ldots\ldots A_1e^{-\lambda_1 t} \quad (1)$$

consistent with a one, two, three or four-compartment open mamillary model.[7] Goodness of fit was determined in each case by calculation of the squared correlation coefficient. The acceptance of a particular

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TABLE 1. Individual Subject Data

	Age (Years), Sex	Weight (kg)	Hematocrit (Per Cent)	Etomidate Dose (mg)	Operation	Duration of Anesthesia (Hours)
Subject 1	42, F	60.0	40	18.0	Atticotomy	3.50
Subject 2	32, F	98.5	40	30.0	Mastoidectomy	3.25
Subject 3	41, M	60.9	48	18.3	Mastoidectomy	5.25
Subject 4	30, M	84.0	45	25.0	Mastoidectomy	3.20
Subject 5	26, F	52.5	41	15.8	Squint correction	1.50
Subject 6	24, M	82.0	41	24.6	Mastoidectomy and tympanoplasty	5.00
Subject 7	18, M	62.5	46	18.8	Exploration tympanotomy and myringoplasty	2.83
Subject 8	26, M	102.0	48	30.0	Exploration tympanotomy, ossiculoplasty and removal of cholesteatoma	2.25
AVERAGE ± SD	29 ± 8	75.3 ± 18.8		22.5 ± 5.6		3.35

equation as the "best" fit was based upon the incremental percentage improvement in the squared correlation coefficient reaching a pre-selected criterion.[8]

In equation 1, the quantity C_p represents plasma etomidate concentration and t represents the time after etomidate injection. The term i is the number of exponential terms required for description of the plasma level decay curve and the number of compartments in the corresponding kinetic model. The coefficients $A_{1,2\ldots i}$ are ordinate axis intercepts, and the exponents $\lambda_{1,2\ldots i}$ are rate constants for each exponential phase. These are "hybrid" quantities influenced by all of the individual processes involved in the disposition of the drug.[9] Half-lives of the disappearance phases, volume of the central compartment (V_c), total apparent volume of distribution by the area method (V_d area), total plasma clearance (Cl_p), first-order rate constants for drug transfer between compartments (k_{12}, k_{21}, k_{13}, and k_{31}), and the elimination rate constant k_{10} were calculated from the coefficients and exponents as described by Gibaldi and Perrier.[9] The fraction of drug in the body that is in the central compartment (λ_3/k_{10}) was also computed.[9] Whole-blood concentrations of etomidate were calculated from the plasma concentrations using the blood/plasma distribution ratio.[5] Total clearance in terms of whole blood was calculated from these derived values. Hepatic clearance was calculated as the product of the total blood clearance and (1 − f), where f is the fraction of the dose excreted unchanged. The hepatic extraction ratio equals hepatic clearance divided by hepatic blood flow.[10]

Results

Plasma levels of etomidate in eight subjects are shown in table 2, and the mean levels are plotted in figure 1. Data from each of the subjects were best fitted to a triexponential equation

$$C_p(t) = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t} + A_3e^{-\lambda_3 t} \quad (2)$$

consistent with a three-compartment open pharmacokinetic model with first-order drug elimination from

TABLE 2. Plasma Levels of Etomidate (ng Base/ml) Following a Single, Intravenous 0.3-mg/kg Dose of Etomidate Sulfate

Time (Hours)	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8	Mean ± SD
0.067	407.0	376.0	260.0	412.0	283.0	221.0	263.0	359.0	322.6 ± 74.3
0.133	208.0	232.0	180.0	223.0	187.0	137.0	174.0	204.0	193.1 ± 30.4
0.25	130.0	162.0	115.0	157.0	150.0	109.0	108.0	144.0	134.4 ± 21.8
0.5	69.1	81.0	88.0	122.0	52.3	81.4	82.8	99.2	84.4 ± 20.5
1.0	46.4	58.4	59.9	68.9	32.7	55.4	49.8	57.8	53.6 ± 10.8
2.0	27.8	35.3	32.5	38.8	21.2	40.6	27.5	35.8	32.4 ± 6.5
3.0	22.5	23.7	21.3	28.8	13.1	28.6	18.1	20.9	22.1 ± 5.2
4.0	18.0	17.3	15.8	23.2	8.0	21.6	12.6	14.4	16.4 ± 4.8
5.0	14.8	11.8	12.6	17.1	5.7	19.3	10.0	10.1	12.7 ± 4.3
6.0	12.9	10.0	11.4	11.7	4.4	17.8	8.9	7.9	10.6 ± 3.9
7.0	11.4	8.6	10.5	10.2	3.9	14.9	7.7	6.3	9.2 ± 3.4
8.0	9.8	7.4	9.9	9.2	3.6	12.5	6.9	5.3	8.1 ± 2.8
9.0	8.4	6.4	9.5	8.3	ND*	ND*	5.7	4.3	7.1 ± 2.0
10.0	7.5	5.5	9.1	7.4	3.2	8.6	4.8	3.5	6.2 ± 2.3

* Not determined.

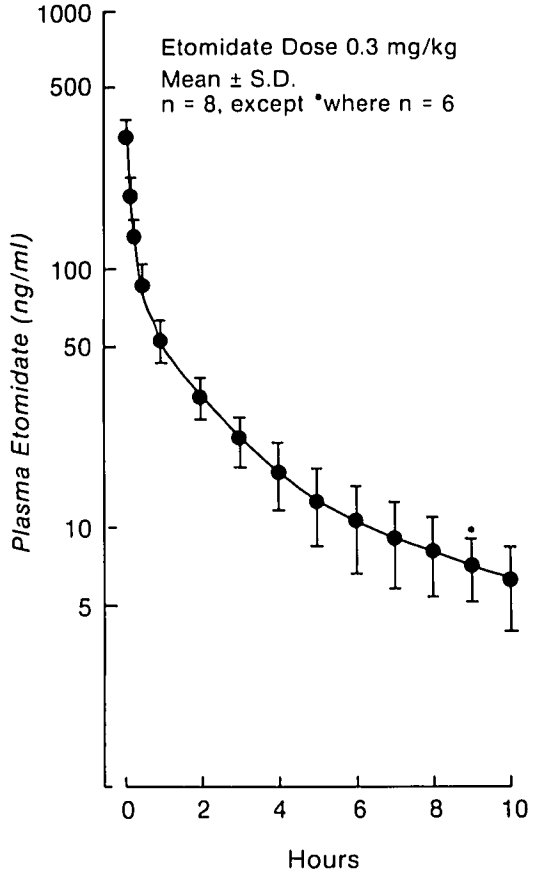

FIG. 1. Plasma levels of etomidate in eight subjects after a 0.3-mg/kg intravenous dose of etomidate sulfate. The line was fitted by computer using non-linear least-squares regression analysis.

the central compartment[9] (fig. 2). The compartments of the model are, of course, apparent compartments and may not correspond to any specific body tissue or fluid. Individual kinetic parameters are shown in table 3. The mean total plasma clearance was 860 ml/min. However, unless the partition ratio of drug between plasma and erythrocytes is high, it is misleading to base any physiologic interpretation on clearance values obtained from data derived from plasma levels.[11] Etomidate is distributed only 62 per cent to plasma in human blood.[5] Mean total clearance in terms of whole blood was 754 ml/min. Since only 2 per cent of etomidate is excreted unchanged,[¶] hepatic clearance was 739 ml/min. Assuming an average value for hepatic blood flow of 1500 ml/min,[12] the hepatic extraction ratio was 0.5 for etomidate.

Discussion

We assessed the distribution and elimination of etomidate as it is used clinically to induce anesthesia. A single intravenous dose of 0.3 mg/kg produces loss of consciousness within 10 sec and a state of anesthesia followed by sleep that lasts approximately 3 to 5 min. The distribution of etomidate is very rapid, since the early exponential phases ($t_{1/2\lambda_1}$ and $t_{1/2\lambda_2}$), generally considered to reflect distribution phenomena, averaged 2.6 and 28.7 min, respectively. This is consistent with rapid penetration into brain tissue, manifested by the rapid onset of anesthesia, and then further, more extensive distribution.

The extent of etomidate distribution is indicated by the fact that the mean total apparent volume of distribution was four and a half times body weight and only 7 per cent of the drug was in the central compartment. This wide distribution is typical of lipid-soluble organic bases such as propoxyphene, propranolol, and pentazocine, and may partly reflect the affinity of these substances for the acidic cellular fluids.[13] Since approximately 75 per cent of plasma etomidate is bound to proteins[5] and only the unbound drug is diffusible, the apparent volume of distribution calculated from total plasma etomidate concentration actually underestimates the extent of distribution.

The rate constants k_{12}, k_{21}, and k_{13}, k_{31} reflect the rate of distribution among compartments of the three-compartment model. The mean ratio of k_{31}/k_{13} of 0.13, reflecting drug movement between the central and deep peripheral compartment, suggests slow equilibration between these compartments. The elimination rate constant k_{10} is on the average six times greater than k_{31}, the rate of return of drug from the deep peripheral compartment. The mean ratio of λ_3/k_{10} of 0.07 indicates that only 7 per cent of the etomidate in the body is in the central compartment, available for elimination at any time. These findings suggest that the return of the drug to the central compartment from the deep peripheral compartment is rate-controlling in the elimination of etomidate.

The apparent elimination half-life of etomidate averaged 4.6 hours, indicating elimination of 15 per cent/hr. This value compares very closely with the 15–19 per cent values reported for thiopental and methohexital.[14]

In preliminary studies of etomidate metabolism in man[¶] using radio-labeled drug, almost 90 per cent of the label eventually appeared in the urine after an intravenous dose, and only 2 per cent was unchanged etomidate, indicating that total clearance of etomidate represents primarily clearance for metabolism. Presumably the site of metabolism is the liver.[15] Hepatic clearance of etomidate was 739 ml/min. The subjects

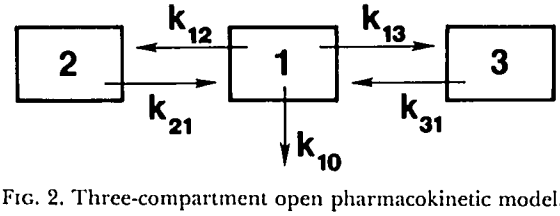

FIG. 2. Three-compartment open pharmacokinetic model.

[¶] Janssen Research Products Information, Janssen Pharmaceutica, Beerse, Belgium.

TABLE 3. Individual Pharmacokinetic Parameters for a Single Intravenous, 0.3-mg/kg Dose of Etomidate Sulfate

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8	Mean ± SD
A_1 μg/ml	1.517	0.554	0.297	1.082	0.383	0.591	0.334	0.910	0.709 ± 0.429
A_2 μg/ml	0.263	0.161	0.117	0.165	0.056	0.099	0.106	0.165	0.142 ± 0.062
A_3 μg/ml	0.042	0.044	0.017	0.047	0.012	0.050	0.022	0.047	0.035 ± 0.015
λ_1 hr^{-1}	32.992	15.912	12.020	24.070	8.425	29.144	12.756	25.905	20.153 ± 9.028
λ_2 hr^{-1}	4.300	2.057	0.935	1.578	0.782	1.999	1.118	2.398	1.896 ± 1.130
λ_3 hr^{-1}	0.185	0.223	0.064	0.198	0.146	0.177	0.153	0.301	0.181 ± 0.068
k_{10} hr^{-1}	5.426	2.439	1.040	3.355	2.262	2.101	1.725	3.845	2.774 ± 1.386
k_{12} hr^{-1}	12.942	6.925	6.168	13.778	3.999	17.112	6.499	13.208	10.079 ± 4.723
k_{21} hr^{-1}	8.836	5.599	4.327	5.063	1.864	7.078	4.246	6.701	5.464 ± 2.119
k_{13} hr^{-1}	9.727	2.695	1.324	3.206	1.000	4.337	1.259	4.125	3.459 ± 2.843
k_{31} hr^{-1}	0.546	0.535	0.159	0.443	0.227	0.692	0.297	0.726	0.453 ± 0.210
$t_{1/2_{\lambda_1}}$ hr	0.021	0.044	0.058	0.029	0.083	0.024	0.054	0.027	0.043 ± 0.022
$t_{1/2_{\lambda_2}}$ hr	0.161	0.337	0.741	0.439	0.886	0.347	0.620	0.289	0.478 ± 0.248
$t_{1/2_{\lambda_3}}$ hr	3.757	3.109	10.864	3.497	4.747	3.915	4.529	2.302	4.590 ± 2.650
λ_3/k_{10}	0.034	0.091	0.061	0.059	0.065	0.084	0.089	0.078	0.070 ± 0.019
V_c (l/kg)	0.118	0.282	0.498	0.165	0.476	0.289	0.464	0.185	0.310 ± 0.152
V_d area (l/kg)	3.454	3.086	8.117	2.800	7.401	3.427	5.249	2.366	4.488 ± 2.196
Cl_p (l/kg/hr)	0.637	0.688	0.518	0.555	1.077	0.607	0.801	0.712	0.699 ± 0.177

were recumbent during the entire experiment, which precluded an effect of posture on hepatic blood flow.[12] Although there is no evidence that nitrous oxide decreases hepatic blood flow,[16] the more potent anesthetic, enflurane, or the combination of enflurane and nitrous oxide could have that effect. On the other hand, these agents were administered only during the first few hours of the study. Assuming a value for hepatic blood flow of 1,500 ml/min,[12] the hepatic extraction ratio is 0.5 for etomidate. Assuming as much as a 27 per cent decrease in hepatic blood flow (1,100 ml/min), the extraction ratio for etomidate would still be in the intermediate range (0.67). Applying the physiologic approach developed by Wilkinson and Shand,[10] this intermediate extraction ratio implies that etomidate clearance will be partly dependent upon, and moderately influenced by, changes in hepatic blood flow and metabolism.

Overall, the kinetic profile is consistent with the concept that etomidate is rapidly distributed within a central compartment and a shallow peripheral compartment which include the brain and highly perfused organs of metabolism, and then to a deeper peripheral compartment. Thereafter etomidate is rapidly eliminated, despite the small fraction of drug in the central compartment, due to its efficient hepatic extraction.

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References

1. Janssen PAJ, Niemegeers CJE, Schellekens KHL, et al: Etomidate, (R-(+)-1-(α methyl-benzyl) imidazole-5-carboxylate) (R16659), a potent, short-acting and relatively atoxic intravenous hypnotic agent in rats. Arzneim Forsch 21:1234–1243, 1971
2. Doenicke A, Kugler J, Penzel G, et al: Hirnfunktion und Toleranzbreite nach Etomidate, einem neuen barbiturat-frein i.v. applizierbaren Hypnoticum. Anaesthesist 22: 357–366, 1973
3. Morgan N, Lumley J, Whitwam J: Etomidate, a new water soluble nonbarbiturate intravenous induction agent. Lancet, 1:955–956, 1975
4. Van Hamme MH, Ambre JJ, Ghoneim MM: Determination of etomidate plasma concentrations by mass fragmentography. J Pharm Sci 66:1344–1346, 1977
5. Meuldermans W, Heykants J: The plasma protein binding and distribution of etomidate in dog, rat and human blood. Arch Int Pharmacodyn Ther 221:150–162, 1976
6. Metzler CM: A user's manual for NONLIN. Technical report 7292/69/7292/005, The Upjohn Company, Kalamazoo, Michigan, 1969
7. Rescigno A, Segre G: Mamillary systems, Drug and Tracer Kinetics. London, Blaisdell Publishing Co., 1966, pp 91–98
8. Sedman AJ, Wagner JG: AUTOAN: A decision-making pharmacokinetic computer program, Publication Distribution Services, 615 East University Avenue, Ann Arbor, Michigan, 1974
9. Gibaldi M, Perrier D: Multicompartments models, Pharmacokinetics. New York, Marcel Dekker, 1975, pp 45–96
10. Wilkinson G, Shand D: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377–390, 1975
11. Rowland M: Influence of route of administration on drug availability. J Pharm Sci 61:70–75, 1972
12. Culbertson J, Wilkins R, Ingelfinger F, et al: The effect of the upright posture upon hepatic blood flow in normotensive and hypertensive subjects. J Clin Invest 30:311, 1951
13. Fingl E, Woodbury D: Pharmacokinetics, The Pharmacological Basis of Therapeutics, Edited by Goodman L, Gilman A. New York, MacMillan, 1975, p 9
14. Brand L, Mark L, Snell M, et al: Physiological disposition of methohexital in man. ANESTHESIOLOGY 24:331–335, 1963
15. Heykants JJP, Meuldermans WEG, Michiels LJ, et al: Distribution, metabolism and excretion of etomidate, a short-acting hypnotic drug, in the rat. Arch Int Pharmacodyn 216:113–129, 1975
16. Cooperman L: Effects of anesthetics on the splanchnic circulation. Br J Anaesth 44:967–970, 1972