Title: THE EFFECT OF INCREASING AGE ON ETOMIDATE PHARMACOKINETICS

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Introduction. Etomidate, a short-acting intravenous anesthetic noted for its hemodynamic stability, is a logical choice for induction of anesthesia in the elderly patient. However, no data is available on the effect of increasing age on etomidate pharmacokinetics. This study was designed to examine that relationship.

Methods. After IRB approval and informed consent, 16 ASA I-II surgical patients, ages 22-80 yrs, weight 83.5 ± 11.9 kg, received etomidate in doses of 26-108 mg by rapid intravenous infusion over 3 to 9 mins. Frequent arterial sampling was used for 2 hrs followed by venous sampling until 12 hrs after induction. Anesthesia was maintained for 3.4 ± 1.5 hrs with N_2O and enflurane. High performance liquid chromatography measurements of whole blood etomidate concentrations were fit by a three-compartment model using extended least squares nonlinear regression. Statistical comparison to a two-compartment model was performed in each case. Kinetic parameters were calculated and related to age by linear regression. Age groups were compared by Student's t-test.

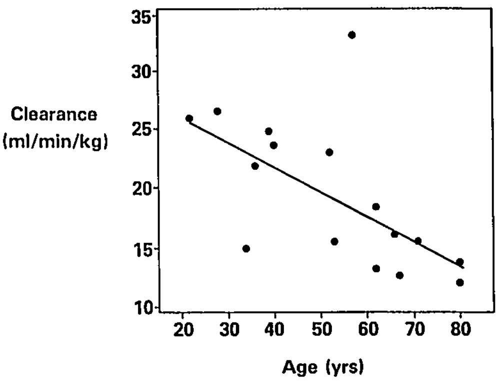
Results. Calculated kinetic parameters for patients greater and less than 65 are shown in Table 1. In all cases, except one, a three-compartment model was statistically preferred. Clearance (CL) of etomidate decreased significantly with age (Fig.1) with r = 0.62 ($p<.01$). Mean CL was significantly lower in patients over 65 ($p<.001$). There was also a significant correlation between age and elimination half-life ($t_{1/2}\beta$). $T_{1/2}\beta$ was longer in patients over 65 ($p<.001$). Central compartment volume (V_1) did not correlate with age nor was V_1 significantly different between the two groups. Volume of distribution at steady state (Vdss), peripheral compartment volumes (V_2, V_3) and distribution rate constants were not significantly correlated with age or different between the two groups. For comparison to other reported CL values whole blood concentration of etomidate, and thus area under the concentration vs. time curve (AUC) can be converted to plasma

TABLE 1. Etomidate Kinetic Parameters - Mean (S.D.)

	Age (yrs)	V_1 (ml/kg)	CL (ml/min/kg)	Vdss (l/kg)	$T_{1/2}\beta$ (min)
Over 65 (N=5)	72 (6.8)	76.9* (30.8)	14.0⁺ (1.8)	4.8 (2.1)	497⁺ (218)
Under 65 (N=11)	44 (13.8)	104.4* (23.6)	22.1⁺ (6.0)	5.8 (3.2)	308⁺ (105)

*p < .005 ⁺p < .001

Figure 1.



concentration (for Hc = 43%) using Cpl = C blood x 1.11. This relationship results from etomidate's greater distribution in plasma than in the RBC (1). Corresponding plasma clearance values are 20.0 ml/kg/min for younger patients (Hc = 43%), and 12.9 ml/kg/min for patients over 65 (Hc = 42%).

Discussion. Changes in drug disposition during aging often include decreased clearance, increased elimination half-life and increased volume of distribution (2). Age-dependent pharmacokinetic changes have been reported for barbiturates, narcotics and benzodiazepines. Since etomidate is a high hepatic extraction ratio drug, its clearance depends on hepatic blood flow. The fact that etomidate clearance falls with age may reflect a progressive decline in cardiac output and renal and hepatic blood flow with age. A prolonged $T_{1/2}\beta$ follows from the change in clearance. These differences may result in longer recovery times in elderly patients after large or repeated doses of etomidate. However recovery after an induction dose of etomidate (0.2-0.4 mg/kg) depends on drug distribution rather than elimination. The absence of a clear correlation with age in V_1 or distribution rate constants in this study would militate against a kinetic explanation for any decrease in dose requirement among the elderly that may be seen clinically. In contrast, older patients have a smaller V_1 for thiopental (3). Etomidate pharmacodynamics deserve investigation in the elderly.

References

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