Title: PHARMACOKINETIC AND PHARMACODYNAMIC MODEL OF ETOMIDATE'S EEG EFFECTS

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Introduction. Though accepted standards exist for assessing effects of inhalation anesthetics (MAC), measurement of brain sensitivity to intravenous anesthetics and narcotics has remained difficult. Recently EEG spectral analysis has allowed estimation of cortical response to thiopental (1) and fentanyl (2). In the present study, EEG spectral edge analysis is applied to etomidate together with a simultaneous pharmacokinetic analysis to construct a dynamic model of brain sensitivity to this drug.

Methods. Following IRB approval and informed consent, 7 ASA I-II male surgical patients, ages 36-62 yrs (mean = 48.4 yrs), weight 80 ± 9.3 kg were studied. After baseline EEG recording, etomidate 7.5-10 mg/min was given by rapid infusion over 3.5-5.5 min until EEG changes previously described for this drug (3) were seen. These consisted of delta waves interrupted by brief periods of low amplitude fast waves. Because of myoclonic EEG artefact during early recovery, patients were transiently relaxed with succinylcholine and ventilated (mean PCO_2 = 41.5) during recording. Frequent arterial samples were obtained during EEG recording until clinical signs of recovery (movement, response to command) were noted. Patients were then anesthetized for surgery. Etomidate concentrations in whole blood were measured by HPLC, and EEG recordings were analyzed to give the spectral edge (SE), the frequency below which 95% of the EEG power lies.

Data Analysis. The simultaneous SE and etomidate levels were fitted by nonlinear regression to a pharmacodynamic or "effect" model described by:

$$SE = E_o - \frac{E_{max} \cdot Ce^{\gamma}}{IC_{50}^{\gamma} + Ce^{\gamma}}$$

Where E_o is the baseline SE (Hz), E_{max} the maximal depression of the SE (Hz), IC50 is the concentration which produces 50% of the maximal SE depression (ng/ml), γ is a dimensionless function reflecting the steepness of the concentraton vs. effect curve, and Ce is the concentration in the "effect compartment", a hypothetical volume which indicates the presence of a time-lag between peak concentration and peak drug effect. This compartment also has an equilibration half-time with blood, $t_{1/2}\ k_{eo}$.

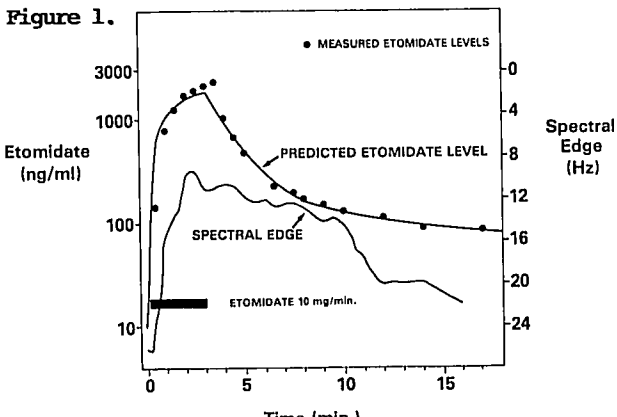
Results. The dose to reach EEG endpoint was .41 ± .12 mg/kg. the relationship between SE and etomidate concentration for a representative patient is seen in Fig. 1. Pharmacodynamic vales for etomidate are seen in the first line of Table 1.

TABLE 1.

	Dose (mg/kg)	Emax (Hz)	IC50 (mcg/ml)	$T^{1}/_{2}$ keo (min)	γ
Etomidate	.411 (.12)	12.5 (3.4)	.35 (.10)	1.8 (0.6)	3.1 (1.6)
Thiopental	9.6 (2.0)	13.7 (2.4)	15.9 (5.1)	1.2 (0.3)	4.5 (3.0)
Fentanyl	.0085 (.0014)	14.1 (1.8)	.0069 (.0015)	6.4 (1.3)	4.8 (1.0)

Discussion. The minimal time lag between peak drug level and peak effect is seen in Fig. 1. This brief delay is quantified by a small $t_{1/2}\ k_{eo}$ for etomidate, similar to that for thiopental, reflecting the rapid onset seen clinically with both drugs. The pharmacodynamic values of etomidate, thiopental and fentanyl using this model are shown in Table 1. The IC_{50} of etomidate relative to thiopental implies a greater brain sensitivity to etomidate on a concentration basis. This IC_{50} value is also in agreement with plasma etomidate values reported by Fragen (4) just prior to awakening. The brain's marked sensitivity to fentanyl is shown by an IC_{50} which is 1/50 that of etomidate. Values of $\gamma > 1$ indicate a steep response to changing concentration for all 3 drugs. Though the clinical correlates with SE have not been defined, this model can provide a continuous, sensitive measure of cortical response to intravenous anesthetics. It has now been successfully applied to different classes of drug and is a powerful tool for comparing drug response in different age groups or in disease states.

Figure 1.



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