Anesthesiology
V 57, No 3, Sept 1982

TITLE: ESTIMATION OF BRAIN SENSITIVITY TO THIOPENTAL WITH THE EEG

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Previously, there have not been direct methods of estimating brain sensitivity to thiopental (TP). In contrast, the concept of MAC has been extensively applied to the inhalational anesthetics. We report the development of a method of estimating brain sensitivity to TP. Power spectrum analysis of the EEG (spectral edge)[1] was used as a measure TP effect. We then used pharmacodynamic modeling concepts to relate the thiopental serum concentration (TpCp) to the spectral edge (SE) of the EEG.

METHODS. Following informed consent and institutional approval, we studied 8 healthy male volunteers, aged 30.3±7.1 (SD) years and weighing 76.6±7.7 kg. TP was infused at 150 mg/min (N=4) or 75 mg/min (N=4) until early burst suppression occurred (phase 3, Fig. 1). Frequent venous blood samples were obtained during and for 20 min after the infusion. TpCp was measured by an HPLC assay. The EEG, recorded on magnetic tape, was processed by a computer using power spectrum analysis to calculate the SE (frequency below which 95% of the EEG power is located).

DATA ANALYSIS. Non-linear regression (NLR) was used to relate the measured TpCp to the SE using the equation:

$$SE = E_o - \frac{E_{max} \cdot TpCp^{\gamma}}{IC_{50}^{\gamma} + TpCp^{\gamma}} \quad \text{where}$$

E_o = the baseline SE, E_{max} = the maximal predicted decrease of the SE induced by TP and γ = a power function. IC_{50} is the predicted TpCp concentration that causes 50% of the maximal decrease of SE and is a direct estimate of brain sensitivity to TP based upon the EEG.

RESULTS. Fig. 2 displays the change of SE and TpCp during and after the infusion. Fig. 3 shows the sigmoid relationship between SE and TpCp. The upper solid line in Fig. 2 and the line in Fig. 3 are the NLR characterization of the SE vs TpCp relationship using the above equation. Since the infusion rate did not influence the results, data from all subjects is presented in the table.

PHARMACODYNAMIC PARAMETERS (mean ± SD)

TP Dose (mg/kg)	E_o (Hz)	E_{max} (Hz)	IC_{50} (µg/ml)
9.6±2.0	24.5±4.2	12.7±5.4	15.9±5.1

DISCUSSION. With a progressively increasing depth of barbiturate anesthesia, the resulting EEG slowing is characterized by the decreased frequency of the SE. The SE changes can be related to the measured TpCp using the above equation. The pharmacodynamic model provides continuous characterization of the relationship between TpCp and the EEG from light (phase 1) to moderately deep (phase 3) TP anesthesia (Fig. 1). The exact relationship of SE to clinical measures of anesthetic depth has not yet been clearly defined. The proposed pharmacodynamic model allows for a baseline SE (E_o) and predicts a maximal effect of TP on the SE (E_{max}). It also provides an estimate of brain sensitivity to TP (IC_{50}) based upon the EEG response. IC_{50} estimates were consistent and independent of the rate of TP administration, with an acceptable inter-subject variability of 30%. By combining pharmacodynamic modeling concepts with the use of the SE as a non-invasive, continuous measure of TP effect, it is now possible to estimate an individual patients' sensitivity to TP.

Fig. 1

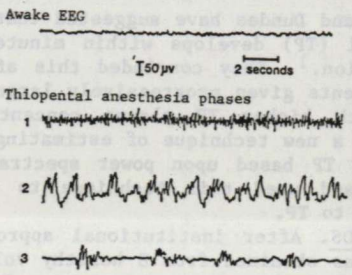


Fig. 2

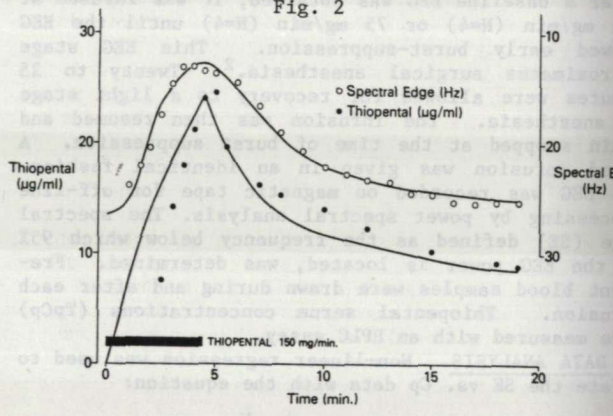
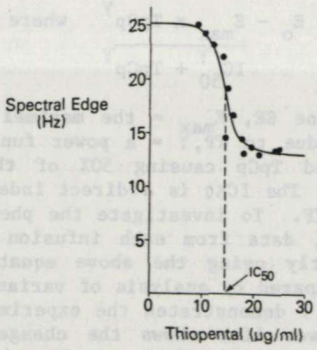


Fig. 3



REFERENCE

1. Rampil IJ, et al: Anesthesiology 53:S12, 1980.