TITLE: DOES ACUTE TOLERANCE TO THIOPENTAL EXIST?

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Toner and Dundee have suggested that tolerance to thiopental (TP) develops within minutes of its administration.[1] They concluded this after observing that patients given progressively larger doses of TP awoke with higher TP plasma concentrations. We developed a new technique of estimating brain sensitivity to TP based upon power spectral analysis of the EEG and used this technique to examine acute tolerance to TP.

METHODS. After institutional approval, informed consent was obtained from 8 healthy volunteers, aged 30.3 ± 7.1 (SD) years and weighing 76.6 ± 7.7 kg. After a baseline EEG was obtained, TP was infused at 150 mg/min (N=4) or 75 mg/min (N=4) until the EEG showed early burst-suppression. This EEG stage approximates surgical anesthesia.[2] Twenty to 25 minutes were allowed for recovery to a light stage of anesthesia. The infusion was then resumed and again stopped at the time of burst suppression. A third infusion was given in an identical fashion. The EEG was recorded on magnetic tape for off-line processing by power spectral analysis. The spectral edge (SE) defined as the frequency below which 95% of the EEG power is located, was determined. Frequent blood samples were drawn during and after each infusion. Thiopental serum concentrations (TpCp) were measured with an HPLC assay.

DATA ANALYSIS. Non-linear regression was used to relate the SE vs. Cp data with the equation:

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

E_o = the baseline SE, E_{max} = the maximal predicted decrease in SE due to TP, γ = a power function, and IC_{50} = predicted TpCp causing 50% of the maximal shift of the SE. The IC_{50} is a direct index of brain sensitivity to TP. To investigate the phenomenon of acute tolerance, data from each infusion was analyzed independently using the above equation. The results were compared by analysis of variance.

RESULTS. Fig. 1 demonstrates the experimental protocol. The lower line shows the changes in TpCp during and after each infusion. The data points around the upper line represent the actual SE. The line is the fitted function using the above equation. Fig. 2 shows the striking similarity between the SE vs. Cp curves for each infusion in the same volunteer. Since there were no significant differences ($P < 0.05$) between the two groups (fast vs. slow infusion) the data from all studies is reported in one table. Comparing the three infusions revealed no significant changes in E_o, E_{max} or IC_{50}.

DISCUSSION. If the subjects were becoming acutely tolerant to the effect of TP on the SE, the IC_{50} during second and third infusions should have been higher than the IC_{50} during the first infusion. This clearly did not occur. The E_o and E_{max} also remained unchanged, providing additional evidence that the relationship between TpCp and the SE was unchanged. We conclude that tolerance to the EEG effects of TP does not develop within a one-hour period.

Fig. 1

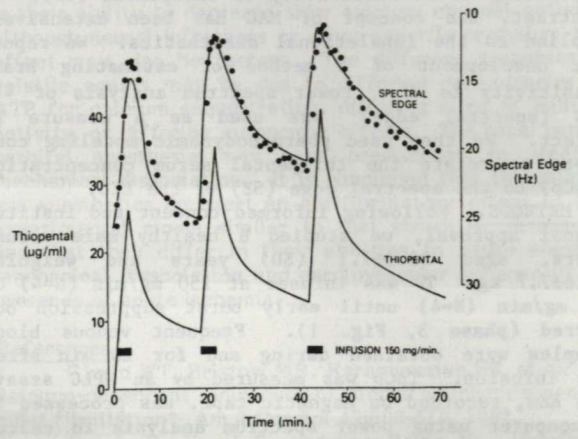
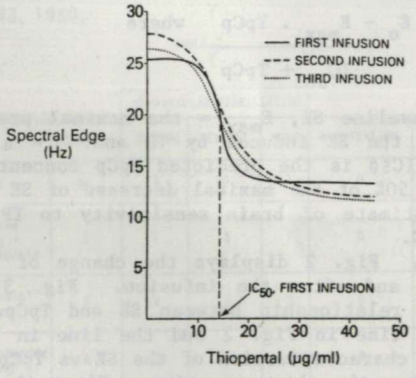


Fig. 2



PHARMACODYNAMIC PARAMETERS
(mean ± SD)

Infusion	1	2	3
Dose (mg.kg)	9.6±20*	5.6±0.9	5.2±1.2
E_o (Hz)	24.5±4.2	25.3±3.9	22.5±4.3
E_{max} (Hz)	13.7±5.4	15.4±5.8	12.8±6.0
IC_{50} (µg/ml)	15.9±5.1	13.9±3.4	16.0±4.4

(*$p < 0.002$, 1st vs. 2nd, 1st vs. 3rd)

REFERENCES.

1. Toner W, et al.: Br J Anaesth 52:1005, 1980.
2. Clark D, et al.: Anesthesiology 38:564, 1973.