Title: DEFINING THIOPENTAL'S STEADY STATE PLASMA CONCENTRATION - EEG EFFECT RELATIONSHIP

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Introduction: A major goal of using the processed EEG in anesthesia is to device non invasive continous measures of CNS drug effects that can be correlated to anesthetic depth. This would allow individualization of drug administration. It has been shown that a relationship exists between thiopental (TP) serum concentrations (Cp) and the degree of EEG slowing[1]. These studies were performed during and after TP infusions when both the Cp and the EEG effect were changing rapidly. Under these non steady state conditions, complicated by equilibration delays between blood and brain, Cp-effect relationships can only be established by using complex models with inherent assumptions. However, measuring directly the true Cp-effect relationship under steady state (SS) conditions (i.e. with constant Cp's over time) obviates the application of complex models. The goal of the present study was to define the true Cp vs EEG effect relationship as a prerequisite for the future calibration of the EEG to TP's clinical depth of anesthesia.

Methods: Following institutional approval and informed consent 6 healthy volunteers (mean age ±SD: 32.3 ±5.1 yrs, mean BW ±SD:74.8±13.4 kg) were studied. The EEG (montage :Fp1/O1, Fp2/O2, Cz/O1, Cz/O2) was recorded and stored on FM tape. After recording 5 min of baseline EEG, a computer driven infusion pump (TIAC[TM], Janssen Scientific) infused TP i.v. at an exponential rate for target levels of 10, 20, 30, 40 mcg/ml (6 min for each level) and in 2 volunteers up to 50 mcg/ml. The time when the subject did not react to verbal stimulus was noted. The infusion was stopped when 3 sec of burst suppression occurred. The TP dose administered ranged from 1025 to 1681 mg. Ventilation was assisted with a face mask when needed. Frequent blood samples were collected and analysed by HPLC. Off-line aperiodic analysis of EEG signals was performed with a Lifescan[TM] EEG Monitor and the parameter "total number of waves" per sec (TNW) was calculated[2,3]. A moving average (window size: 30 sec, step size: 1 sec) was used for the graphic display of TNW. Mean values for measured Cp and TNW during the different target infusions were calculated for the last 3 and 2 min, respectively.

Results: The infusion pump provided stable Cp's over time. A stable value (fig. 1, shaded area) for the pharmacodynamic effect (TNW) was achieved after an equilibration time of 2-3 min for each target Cp. This reflects the true SS Cp-effect relationship for the chosen Cp. The biphasic nature (excitation and inhibition) of TP is characterized by an increasing, then decreasing effect value with increasing Cp's (fig. 1 and 2). Because of this biphasic effect the baseline TNW value can also occur with a TP Cp of 20 to 40 mcg/ml where moderately deep anesthesia is present. However, effect values lower than baseline are correlated only with TP Cp's of 40 to 60 mcg/ml. All subjects fell asleep when TNW reached the peak value, either before or on the 20 mcg/ml TP target level (mean measured concentration: 19.9

mcg/ml, table 1). TP Cp's needed to suppress response to noxious stimuli (40 to 60 mcg/ml)[4] would be associated with a TNW of 0 to 5/sec.

Discussion: We have been able to define a biphasic steady state TP Cp-EEG effect relationship using the TNW as an EEG parameter. Loss of consciousness occured at an activated EEG (increased TNW). Constant TP Cp's result into constant EEG effects, both during activation and slowing of the EEG. This infusion technique in combination with continuous effect measurements will permit calibration of anesthetic depth with EEG in the presence of appropriate stimuli.
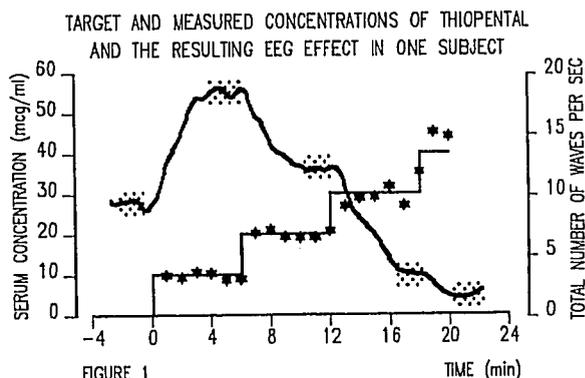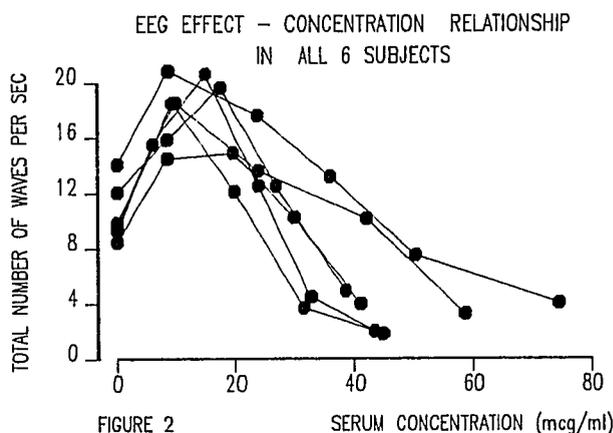
TARGET AND MEASURED CONCENTRATIONS OF THIOPENTAL
AND THE RESULTING EEG EFFECT IN ONE SUBJECT

FIGURE 1   TIME (min)

EEG EFFECT - CONCENTRATION RELATIONSHIP
IN ALL 6 SUBJECTS

FIGURE 2   SERUM CONCENTRATION (mcg/ml)

table 1: target TP Cp's and mean measured Cp's
         (mean ±SD, mcg/ml)

target Cp:	10	20	30	40	50
meas. Cp:	8.5±1.3	19.9±3.5	31.6±6.5	44.3±9.2	52.1
(n)	(6)	(6)	(6)	(6)	(2)

References:
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1. Smith NT et al. J Clin Monit 1: 236-244, 1985
2. Gregory TK et al. J Clin Monit 2: 190-197, 1986
4. Becker KE. Anesthesiology 49: 192-196, 1978