Subject: A CHRONICALLY INSTRUMENTED RAT MODEL FOR COMBINED PHARMACOKINETIC AND CNS PHARMACODYNAMIC ASSESSMENT OF ANESTHETICS

Authors: W.F. EBLING, Ph.D., A.G.L. BURM, Ph.D., J. FIELD, ASc., D.R. STANSKI, M.D.

Affiliation: Department of Anesthesia, Stanford University, Stanford, CA 94305 and Veterans Administration Medical Center, Palo Alto, CA 94304

Introduction: Estimating both the anesthetic depth and neurophysiologic state are major aims of intraoperative EEG monitoring. Achieving this ambitious goal will require an understanding of how anesthetics and surgery interact on underlying EEG mechanisms. For ethical reasons much of this information will have to be obtained from animal models which are consistent with clinical observations. As a first step towards this goal we have developed chronically instrumented rat model that allows simultaneous collection of high resolution pharmacokinetic(Pk) and EEG pharmacodynamic(Pd) data. Thiopental(Tp) data obtained in this model are presented below.

Methods: Under ketamine anesthesia eight EEG electrodes were implanted in the skull of seven male wistar rats(325-350Gm). One week later a jugular catheter was inserted for drug infusion under isoflurane anesthesia. An aortic catheter was implanted for Tp blood sampling through the caudal tail artery Animals were allowed to recover from surgery for 24 to 48 hours. On the day of the study EEG leads were attached to recording instruments and EEG recorded for off-line processing and analysis. Tp was infused at 16mg/kg/min until 5 seconds of isoelectricity was observed. Multiple arterial blood samples(200 ul) for Pk assessment were obtained before and after infusion. Blood sampling and EEG recording continued for 3 hours from the start of the infusion Samples were frozen at -20° C until assayed by HPLC. Rectal temperature was maintained at 38° ± 0.5 during the study. Off-line, EEG signals were processed with aperiodic analysis using the Lifescan^{Tm} EEG monitor and data acquisition/analysis software. The total number of EEG waves per second[1] (TNW) was used as a univariant discriptor of EEG drug effect.

Results: All animals achieved isoelectric EEG in less then 3.5 minutes of Tp infusion. Representative EEG patterns during the infusion are shown in Figure 1. Shortly after the beginning of infusion EEG activity increases in frequency and amplitude. By 2 minutes EEG events decrease until "burst suppression" appears as shown at 3 minutes. EEG recovered to baseline by 3 hours; animals were freely moving at this time. Tp plasma concentration and EEG effect time profiles are shown for a representative animal in Figure 2. Tp concentrations decay in a polyexponential manner following the short infusion. The biphasic character of the TNW time course characterizes the activation and depression of the Tp EEG illustrated in Figure 1. The reactivation of the EEG parallels the declining terminal plasma elimination phase of Tp. Lines represent the best fit to a tentative biphasic Pk/Pd model[2] of Tp EEG effect. The normal variability of the fundamental Pk parameters of Tp disposition listed in Table 1 illustrate the quality of data obtainable from this model.

Discussion: The chronically instrumented rat is a suitable and inexpensive model for obtaining plasma drug concentration and effect data of sufficient quality and quantity for high resolution Pk/Pd investigations of anesthetic action. The data presented here is consistent with the Tp EEG effect time course described in humans[3]. Obtaining whole animal drug effect data will complement tissue concentration data not normally available from humans and provide insight into anesthetic effect site Pk/Pd. Perturbing hemodynamics in this model permits an examination of the effect of altered physiology on Pk/Pd. We are using this model to study the Pk/Pd of barbiturates, narcotics and vapor anesthetics.

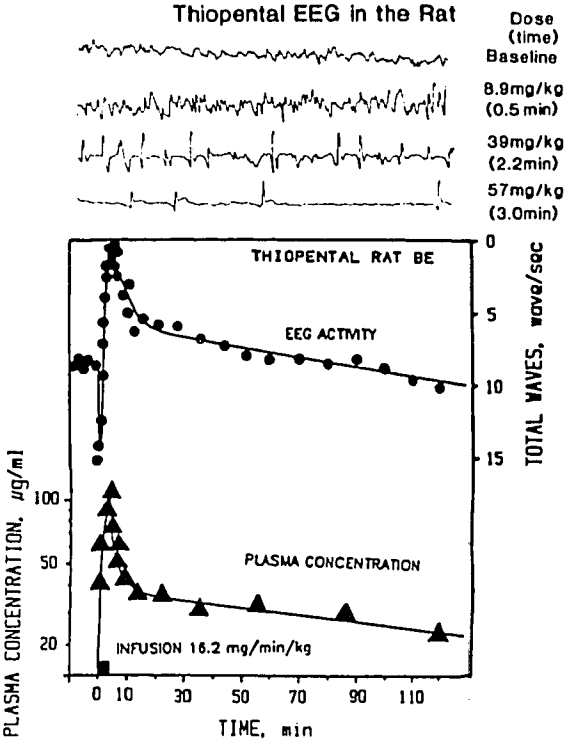

TABLE 1. THIOPENTAL PHARMACOKINETICS IN THE RAT

Elimination Clearance, ml/min/kg	4.15[a]	(34.2)[b]
Distribution Clearance, ml/min/kg	246	(17.7)
Steady-State Volume, ml/kg	1280	(20.7)
Central Volume, ml/kg	79.4	(36.9)
Mean Residence Time, min	335	(32.2)
Half-Life, min	238	(32.6)

a. Mean, N=7 b. % Coefficient of variation

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