CLINICAL INVESTIGATIONS

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Thiopental Pharmacodynamics

I. Defining the Pseudo–Steady-state Serum Concentration–EEG Effect Relationship

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To assess depth of anesthesia for intravenous anesthetics using clinical stimuli and observed responses, it is necessary to achieve constant serum concentrations of drug that result in constant biophase or central nervous system concentrations. The goal of this investigation was to use a computer-controlled infusion pump (CCIP) to obtain constant serum thiopental concentrations and use the electroencephalogram (EEG) as a measure of thiopental's central nervous system drug effect. The number of waves per second obtained from aperiodic waveform analysis was used as the EEG measure. A CCIP was used in six male volunteers to attain rapidly and then maintain for 6-min time periods the following pseudo–steady-state constant serum thiopental target concentrations: 10, 20, 30, and 40 μg/ml. The median performance error (bias) of the CCIP using 149 measurements of thiopental serum concentrations in six subjects was +5%, and the median absolute performance error (accuracy) was 16%. Following the step change in serum thiopental concentration, the EEG number of waves per second stabilized within 2–3 min and then remained constant until the target serum thiopental concentration was changed. When the constant serum thiopental concentration was plotted against the number of waves per second for each subject, a biphasic serum concentration *versus* EEG effect relationship was seen. This biphasic concentration:response relationship was characterized with a nonparametric pharmacodynamic model. The awake, baseline EEG was 10.6 waves/s; at peak activation the EEG was 19.1 waves/s and occurred at a serum thiopental concentration of 13.3 μg/ml. At a serum thiopental concentration of 31.2 μg/ml the EEG had slowed to 10.6 waves/s (back to baseline) and at 41.2 μg/ml was 50% below the baseline, awake value. Zero waves per second occurred at serum thiopental concentrations > 50 μg/ml. Using a CCIP it is possible to establish constant serum thiopental concentration rapidly and characterize the concentration *versus* EEG drug effect relationship. (Key words: Anesthetics, intravenous: thiopental. Brain: electroencephalography. Equipment: computer-controlled infusion pump. Pharmacodynamics: thiopental.)

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WHEN THIOPENTAL IS GIVEN as an intravenous (iv) bolus or infusion, the serum concentrations will change rapidly during and immediately after administration because of drug distribution between blood and body tissues. This distribution/redistribution process is governed by the cardiac output, regional blood flow, and tissue:blood solubility.[1] The redistribution of thiopental from the central nervous system (CNS) to muscle and fat tissue is responsible for the short duration of hypnotic effect following single-dose administration. The concentration of drug in the CNS and the effect related to this concentration will lag behind the serum concentrations of thiopental because the transfer of drug from blood to the effect site in the CNS is not instantaneous.

The electroencephalogram (EEG) provides a continuous, noninvasive indirect measure of drug effect. By combining EEG analysis with frequent measurement of serum thiopental concentrations, it is possible to model mathematically the relationship between serum concentration and drug effect.[2,3] Using this methodology, the half-time of blood:brain equilibration for thiopental has been estimated to be 1–2 min.[3–5] While the EEG is a reflection of drug effect on the brain, its clinical significance for the assessment of anesthetic depth is not clear. Numerous investigators have attempted to examine this issue with limited success.[6–10]

To assess clinical depth of anesthesia, it is usually necessary first to apply some form of stimulus (usually noxious) and then observe a clinical response.[11] For the inhalational anesthetic drugs, the minimum alveolar concentration concept uses skin incision as the stimulus and purposeful movement as the clinical response.[12] A finite period of time is necessary for application of the stimulus and observation of the clinical response. It is essential that during this time the anesthetic drug concentration be kept

at a constant level. The minimum alveolar concentration concept uses a fixed, end-tidal inhalational anesthetic partial pressure that results in partial pressure equilibration between blood and brain and maintenance of that partial pressure between application of the skin incision and observation of the move/no move response.

If a given response to drug is to be measured for an iv anesthetic like thiopental, then it is essential that methodology exist to achieve rapidly and then maintain constant serum drug concentrations that will equilibrate with the site of action in the CNS. Rapidly changing drug concentrations, as would occur following an iv bolus injection, result in disequilibrium between the serum and CNS concentrations that render the observed clinical responses uninterpretable. Rapidly attainment and then maintenance of constant serum concentrations for iv anesthetics can be achieved with computer-controlled infusion pumps (CCIPs).[13–15]

The goal of this study was to use the CCIP to overcome the impediments arising from the rapid distribution pharmacokinetics of thiopental and the delay in blood–effect site equilibration. The CCIP and available thiopental pharmacokinetic data were used to attain rapidly and then maintain multiple pseudo–steady-state serum thiopental concentrations in human subjects. The serum concentrations are termed pseudo–steady-state (hereafter termed constant) because blood:tissue equilibration will occur only with tissue having high perfusion (*i.e.*, vessel-rich tissues such as the brain) in the short period of time (30 min) of the study. Total body equilibration (including poorly perfused tissues) would require several hours of a constant serum thiopental concentration. The EEG was used to monitor thiopental's CNS drug effect and to examine the blood:brain equilibration. In previous studies we used the spectral edge EEG parameter obtained from a fast Fourier waveform (FFT) analysis[2–5] to measure thiopental's CNS drug effect. In the current study, we used the number of waves per second obtained from aperiodic waveform analysis. In the Appendix, we present our data and reasoning for choosing the waves per second as the EEG parameter. This study defined the constant serum thiopental concentration *versus* EEG number of waves per second relationship in human subjects.

Materials and Methods

Institutional approval and informed consent were obtained from 9 healthy male subjects. All subjects (3 surgical patients and 6 volunteers) were free of medication and had normal results on routine laboratory screening. No premedication was given prior to the experiments.

Electroencephalogram Recording

Bipolar EEG was recorded on leads Fp1-O1, Fp2-O2, Cz-O1, and Cz-O2 according to the international 10/20 system of electrode placement. After gentle scrubbing of the scalp with an abrasive solution (Omniprep®, D. O. Weaver Co., Aurora, CO), silver disc electrodes (IMA Electronics, Gainesville, FL) were attached with sticky electrode cream. The electrodes were connected to the EEG recorder (Nihon Kohden® model 5210, Nihon Kohden, Inc., Irvine, CA), using default settings (high-frequency filter 70 Hz, time constant 0.3 s, sensitivity 10 μV/mm). The impedance on the electrodes was less than 3,000 ohm. Calibration signal (50 μV) and EEG was recorded on paper and frequency-modulation magnetic tape (TEAC® Data Recorder R-71, TEAC Corp. of America, Montebello, CA) for subsequent off-line analysis. Baseline (predrug) EEG was recorded for at least 5 min. The subjects kept their eyes closed during baseline recording. Following the thiopental administration the EEG was recorded for 30–90 min, until the subjects were awake, alert, and no longer able to lie comfortably on the operating room table.

Electroencephalogram Analysis

Aperiodic waveform analysis[16] was performed on a Lifescan® Research System (Diatek Corporation, San Diego, CA), consisting of an EEG Monitor and a 286-based IBM personal computer clone. The analog signal stored on tape was first digitized at a sampling rate of 960 Hz. Sequential 1-s epochs of the signal were then subjected to aperiodic analysis. Aperiodic analysis splits the EEG waveform into units of consecutive trough–peak–trough waves or events, determines the corresponding wavelength of the event, and calculates the peak-to-peak voltage or amplitude of the event. Amplitudes of waves smaller than 8 μV are not detected by the algorithm. It then creates a spectra (matrix) of frequency (1 Hz bins) *versus* 1) amplitude and 2) number of waves at 1-s intervals. The total number of waves per second was calculated over the complete 1–30-Hz frequency range at 1-s intervals. The EEG parameter was smoothed using a moving average over 60 s. No other data editing was performed. The appendix presents data that indicates our choice of the waves per second as a useful EEG parameter.

Computer-controlled Administration of Thiopental

To achieve constant serum concentrations we used a CCIP (TIAC®, Janssen Scientific, Beerse, Belgium).[13] The pump administered the drug as a loading bolus dose with an exponentially declining infusion rate. The loss of drug from blood due to tissue distribution can be compensated for by this infusion scheme. The pharmacokinetic parameters used in the CCIP were obtained by fitting a biexponential pharmacokinetic model to the first 40 min of the serum thiopental concentration *versus* time curves of 28 subjects aged 23–88 yr as previously reported by

TABLE 1. Pharmacokinetic Parameters for the Two-compartment Model Used in Computer-driven Infusion Pump

Rate constant α	0.940 min^{-1}
Rate constant β	0.045 min^{-1}
Intercept A	110 $\mu g/ml$
Intercept B	16 $\mu g/ml$
Corresponding thiopental dose (free acid)	500 mg

Homer and Stanski.[4] Nonlinear least squares regression (MKMODEL)†† was used for each individual. The slopes and intercepts of each subject were averaged to create the pharmacokinetic parameters presented in table 1 that were used in the CCIP.

COMPUTER-CONTROLLED INFUSION PUMP PERFORMANCE ANALYSIS

To characterize the performance of the CCIP in achieving the target serum thiopental concentrations, the percent performance error (PE) was defined as:

$$PE = \frac{(C_M - C_T)}{C_T} \times 100\%$$

where C_M was the measured serum thiopental concentration and C_T was the target concentration predicted by the CCIP. The median performance error ($\overline{MDPE}$) for the population was then calculated as the mean of the median PE (MDPE) for each individual:

$$\overline{MDPE} = \frac{\sum_{i=1}^{n} \text{median}\,(PE_{i,1}, PE_{i,2}, \cdots, PE_{i,j_i})}{n}$$

where n was the total number of subjects and j_i was the number of samples for the ith subject. The population $\overline{MDPE}$ is a measure of the systematic bias (*i.e.*, systematic over- or underachievement of the target level) by the CCIP.

The median absolute performance error ($\overline{MDAPE}$) for the population was calculated as the mean of the median absolute PE (MDAPE) for each individual:

$$\overline{MDAPE} = \frac{\sum_{i=1}^{n} \text{median}\,(|PE_{i,1}|, |PE_{i,2}| \cdots, |PE_{i,j_i}|)}{n}$$

where n and j_i are as described for the $\overline{MDPE}$. The population $\overline{MDAPE}$ is clinically easy to interpret in that half of the performance errors will be smaller and half will be larger than the $\overline{MDAPE}$. These measures of CCIP performance have been presented in detail previously.[14,15]

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PILOT STUDY

Changes in the EEG drug effect could be caused by variation in the serum concentrations and/or by an inherent instability of the EEG effect parameter over time. This preliminary study explored in three patients (age 38–62 yr; body weight 61–97 kg) the performance of the infusion pump and the stability of the EEG drug effect in the presence of constant serum thiopental concentrations maintained for at least 10 min at one target level. Thiopental was infused to achieve target levels of 15 $\mu g/ml$ for 10 min in pilot subject A (20 $\mu g/ml$ in subjects B and C), followed by a target level of 30 $\mu g/ml$ (40 $\mu g/ml$ in subjects B and C) for 10 min.

MULTIPLE TARGET LEVEL STUDY

The CCIP administered thiopental to achieve rapidly and maintain a stepwise series of target levels in six healthy volunteers (age 25–39 yr; body weight 62–99 kg). Each target concentration was maintained for 6 min, since the pilot study demonstrated stability of serum concentrations over 10 min and equilibration between serum and effect site (EEG) occurring within 2–3 min. The thiopental target concentrations to be achieved were 10, 20, 30, and 40 $\mu g/ml$ in each subject. In two subjects, burst-suppression had not occurred after 6 min of the 40-$\mu g/ml$ plateau concentration. In these subjects (HO, PE), an additional target thiopental plasma concentration of 50 $\mu g/ml$ was achieved and maintained for 6 min. The CCIP achieved the target thiopental concentration within 1 min and then maintained it for up to 6 min, creating a "square wave" of drug concentration. The infusion was stopped when 3-s periods of isoelectric EEG were noted.

The thiopental target concentrations were achieved sequentially beginning with the lowest and increasing to the highest value. It was not possible to randomize the target concentrations or to "step down" the concentrations because of the additional time necessary to allow the thiopental concentration to decline and the marked increase of the total thiopental dosage.

Thiopental was infused in an antecubital vein. A radial artery was cannulated for arterial pressure monitoring and for blood sampling to measure drug concentrations and blood gases. Oxygen was given by face mask during baseline recording and until the subject recovered from the drug effect. Ventilation was assisted to keep arterial P_{CO_2} within physiologic range. During the infusion, samples were collected every minute. Serum was stored at −20° C until subsequent analysis. Serum thiopental concentrations were measured by a previously reported high-performance liquid chromatography assay.[17]

Before and during the drug administration, the subject's response to verbal command was assessed every 15 s by the command to "move your toes." The time of the

last response and of the first nonresponse to this verbal stimulus was noted.

Pharmacodynamic Data Analysis

A nonparametric pharmacodynamic modeling approach as proposed by Ebling *et al.*[18] was used to characterize the biphasic relationship between constant serum thiopental concentrations and the EEG number of waves per second. Nine parameters are used in this model:

1. Baseline number of waves per second while awake
2. Total area under the curve (AUC) of the thiopental concentration *versus* number of waves per second relationship
3. Percent of the AUC that represents EEG activation, above the baseline, awake value
4. Serum thiopental concentration at the centroid (50%) of the total AUC
5. number of waves per second at the centroid
6. Serum thiopental concentration at the peak of EEG activation
7. Number of waves per second at the peak of EEG activation
8. Serum thiopental concentration at the baseline EEG effect
9. Serum thiopental concentration at 50% of the EEG baseline.

Figure 1 displays the conceptual approach to describing a biphasic drug concentration *versus* drug response relationship using the previously indicated pharmacodynamic descriptors. Each subject's constant serum thiopental concentration *versus* number of waves per second relationship was characterized with a polynomial interpolating spline. From the polynomial function, the nine descriptors indicated above were calculated for each subject and the mean values for the group estimated.

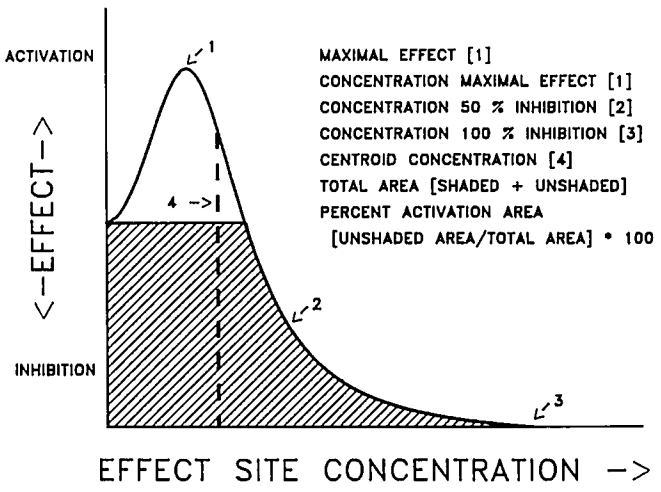

FIG. 1. Descriptors of the biphasic relationship between drug concentration and EEG effect including the concentrations at certain defined EEG endpoints (points 1–4), maximal activation of the EEG (point 1), and the total and activation areas described by the relationship. (Reproduced from Ebling *et al.*,[18] with permission.)

TABLE 2. Hemodynamic Parameters and Arterial Blood Gases in Six Subjects with Pseudo-Steady-state Infusion of Thiopental until Burst Suppression

	Mean Arterial Pressure		Heart Rate	
	Median (mmHg)	Range (mmHg)	Median (min^{-1})	Range (min^{-1})
At baseline	106	95–116	66	54–81
At burst suppression	86	73–100	83	75–90
	P_{O_2}		P_{CO_2}	
	Median (mmHg)	Range (mmHg)	Median (mmHg)	Range (mmHg)
At burst suppression	565	519–593	44	30–54

Results

All studies were completed without any clinically significant complications. Upon regaining consciousness, three subjects experienced nausea and vomiting. Hemodynamically, the infusion of thiopental (total dose 1,025–1,681 mg) caused some decrease of the mean arterial blood pressure (table 2). These changes were not clinically or statistically significant. The arterial P_{CO_2} at the time of maximal EEG slowing (burst suppression) ranged from 30 to 54 mmHg.

Figure 2 displays representative pilot subject raw EEG and the number of waves per second at a constant target serum thiopental concentration of 20 μg/ml. The individual number of waves per second are displayed along with a 60-s smoothing function. Note the transient EEG activation that occurs in the first few minutes of drug administration.

Figure 3 displays the individual subject's measured serum thiopental concentration *versus* time at the different pseudo-steady-state target concentrations. Data beyond 40 μg/ml for the two subjects who received 50 μg/ml target concentrations are not displayed. While there is moderate interindividual variability between the measured and target serum thiopental concentrations immediately after changing the level, the serum concentrations measured for each subject become stable within 3–4 min at each target level. The difference between measured and target thiopental serum concentrations had a tendency to increase at the highest target level (40 μg/ml). Figure 4 displays the percent performance error for each subject over time. In the six subjects a total of 149 measured arterial serum thiopental concentrations were obtained. The population MDPE was +5%, and the population MDAPE was 16%.

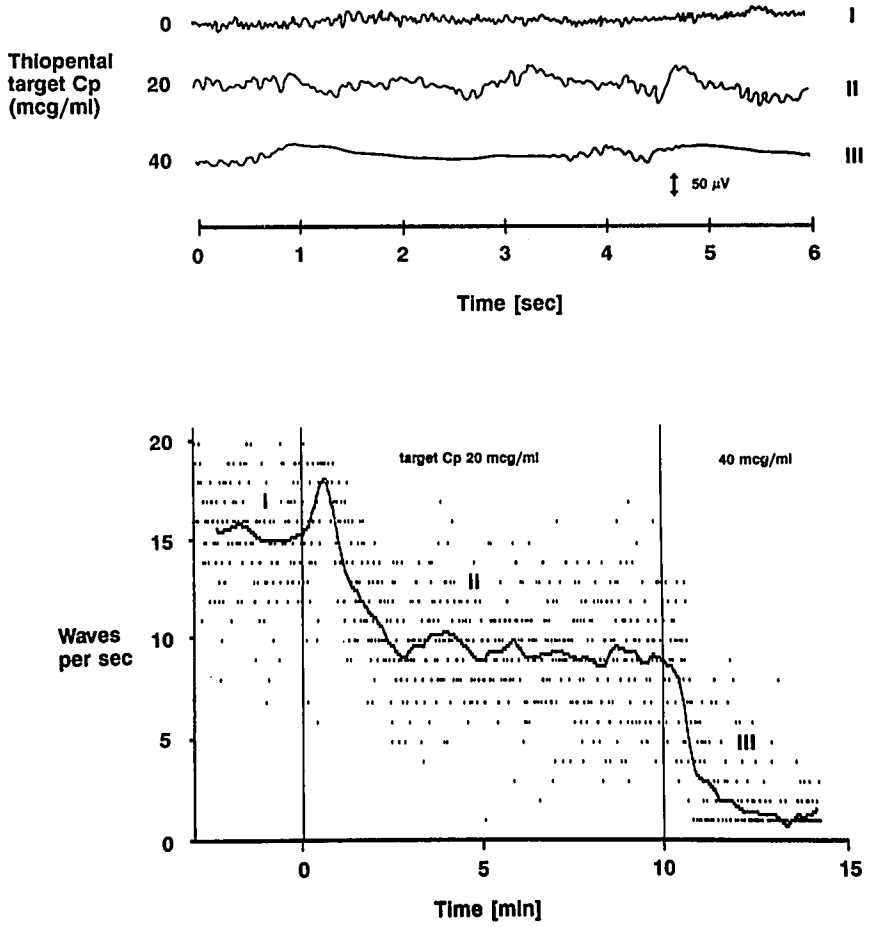

FIG. 2. A representative example of pilot study subject C's raw EEG and the aperiodic analysis parameter number of waves per second. *Top:* Raw normal EEG (I) during baseline (predrug), EEG slowing (II) at a target thiopental level of 20 μg/ml, and burst suppression (III) at a target thiopental level of 40 μg/ml. *Bottom:* Processed EEG, showing the behavior of the number of waves corresponding to the above displayed raw EEG (I–III). After a short period of EEG activation, the parameter stabilizes within 2–3 min and remains stable for the remaining 7 min of the first target level period; 2–3 min after initiation of the second target level, the averaging parameter approaches values of 1 wave/s. Each dot represents the number of waves in a particular second; the solid line represents the values obtained by using a 60-s moving average (smoothing).

The serum–effect site equilibration can be demonstrated for different stages of the biphasic thiopental EEG effect (activation and then slowing). Figure 5 displays the number of waves per second *versus* time relationship and the serum thiopental concentration (measured and target) *versus* time for subject SU. The equilibration of the EEG effect occurs within 2–3 min after a change in the target serum thiopental concentration. Figure 6 and table 3 display the mean constant serum thiopental concentration and EEG number of waves per second measured in the

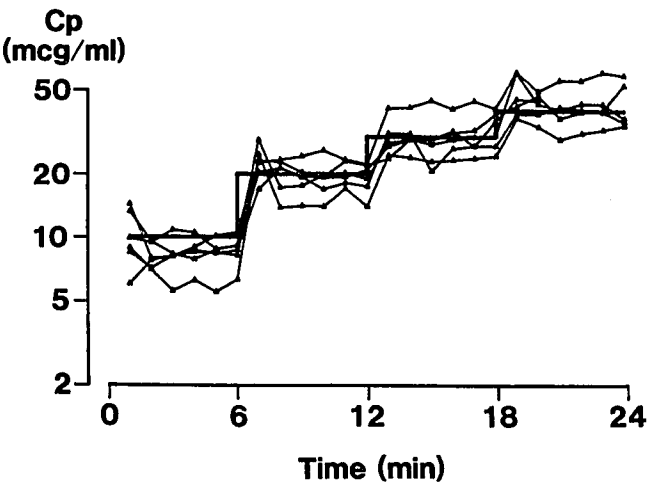

FIG. 3. Measured serum thiopental concentration (Cp) *versus* time profiles from the six volunteers relative to the target concentrations.

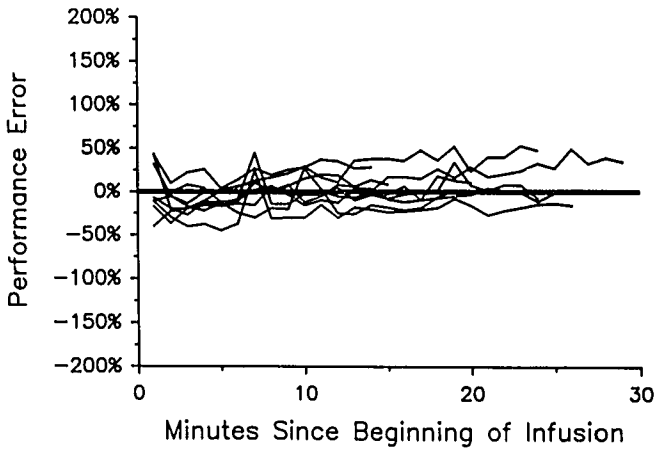

FIG. 4. The individual subject performance error (%) over time. The performance error indicates by what percent the measured thiopental concentration was higher or lower than the target concentration.

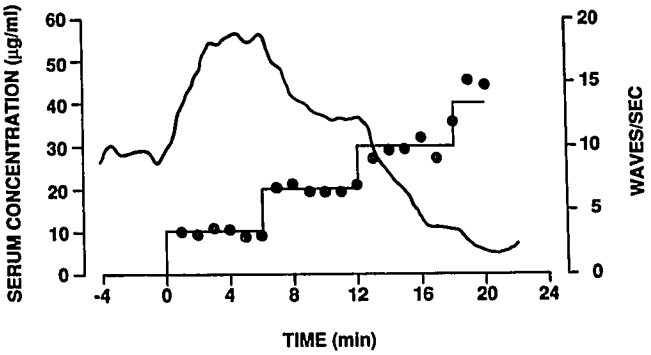

FIG. 5. Serum concentrations *versus* time and EEG drug effect (number waves) *versus* time profiles in subject SU. Thiopental was infused by a computer-controlled infusion pump to obtain constant serum concentrations (closed circles) at defined multiple target levels (staircase line). Note the biphasic EEG effect: at concentrations of 10 μg/ml, the number of waves increases from baseline values of 10 waves/s to an activation values of 20 waves/s; at higher concentrations the number of waves per second is decreasing.

last 3 min of each target concentration for each subject.

Table 4 presents the nine descriptors of the biphasic serum thiopental concentration *versus* number of waves per second relationship presented in table 3 and figure 6.[18] The mean awake, baseline was 10.6 waves/s. The maximal EEG activation was 19.1 waves/s and occurred at an average measured serum thiopental concentration of 13.3 μg/ml. The baseline value of 10.6 waves/s was achieved at an average serum thiopental concentration of 31.3 μg/ml, and a 50% decrease of the baseline number of waves per second occurred at an average serum thiopental concentration of 41.0 μg/ml. Of the total AUC for the relationship of serum thiopental concentration *versus* number of waves/s, 25.8% was associated with EEG activation above the awake baseline and the remainder with EEG slowing below the baseline. The centroid, or 50% of the AUC, occurred at a mean serum thiopental concentration of 21.8 μg/ml and at 15.8 waves/s. The subjects became nonresponsive to verbal commands when the plateau of maximal EEG activation was reached (responsive up to 4.75–8.75 min, nonresponsive at 5.0–9.0 min).

Discussion

The goal of this study was to develop methodology that would allow one rapidly to obtain constant serum thiopental concentrations that result in a stable drug effect. With serum thiopental concentrations constant, after an appropriate period of time for blood:brain equilibration, one could achieve relatively constant biophase or site of action thiopental concentrations. In the current study, we used a CCIP to obtain the thiopental dosing pattern necessary to achieve constant serum concentrations. We used the EEG changes induced by thiopental to examine indirectly the biophase or site of action kinetics relative to the methodological goals proposed.

With the thiopental pharmacokinetic data used in the CCIP, it was possible to obtain constant serum concentrations (fig. 3). The $\overline{\text{MDPE}}$ of +5% indicated no systematic bias in the measured concentrations. The $\overline{\text{MDAPE}}$ of 16% indicates that 50% of the measured levels were within 16% of the desired target level. The predictive performance seen with thiopental in the CCIP (fig. 4) is comparable to what has been obtained with alfentanil[15] ($\overline{\text{MDPE}}$ of +1% and $\overline{\text{MDAPE}}$ of 17%) and fentanyl[14] ($\overline{\text{MDPE}}$ of −13%, $\overline{\text{MDAPE}}$ of 21%). The pharmacokinetic data used in this study were derived from the first 40 min of thiopental distribution pharmacokinetics from one of our previous studies[4] because our current study design did not involve administration of thiopental for a period of time longer than 40 min. We previously demonstrated that age and body weight are factors that explain thiopental pharmacokinetic variability.[5] However, the volunteers in this study were of a very narrow age and body weight range, so we did not adjust the pharmacokinetic data for these factors. The excellent predictive performance seen with our data could not have been improved greatly using patient covariates for the pharmacokinetics.

We examined the pharmacologic effect using the continuous measure of the EEG. The pilot studies (fig. 2) demonstrated that the EEG effect site rapidly equilibrated with the serum concentration within 2–3 min and that the EEG drug effect then remained constant in the presence of constant serum concentrations. This equilibration time is predicted from the half-time of blood:brain equilibration value of 1–2 min previously measured for thiopental.[3–5] First-order processes predict that 90% of equilibration will occur within three to four half-times. We previously presented a more formal analysis and discussion of the serum thiopental concentration:effect site equilibration process using the "square wave" and zero-order infusion approaches.[19]

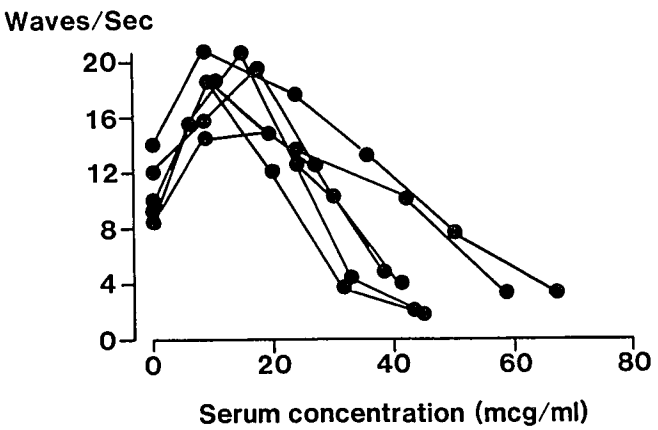

FIG. 6. The EEG drug effect (waves per second) *versus* constant serum thiopental concentration profiles from the six subjects.

TABLE 3. Measured Serum Thiopental Concentrations and Corresponding EEG Effect (waves per second) from Pseudo–Steady-state Study in Six Subjects

Target concentration (μg/ml) / Time (min) / Subjects		0.0 <0	10 0–6	20 6–12	30 12–18	40 18–24	50 >24
AL	Cm (μg/ml)	0.0	6.0	15.0	23.8	32.7	42.7*
	Waves/s	9.4	15.6	20.7	12.6	4.5	2.0*
HO	Cm (μg/ml)	0.0	8.5	17.5	26.8	38.5*	—
	Waves/s	12.1	15.9	19.7	12.5	5.0*	—
DO	Cm (μg/ml)	0.0	8.6	19.6	29.9	41.0*	—
	Waves/s	8.5	14.5	15.0	10.3	4.0*	—
TU	Cm (μg/ml)	0.0	9.9	23.8	42.0	58.6*	—
	Waves/s	9.9	18.6	13.6	10.2	3.3*	—
PE	Cm (μg/ml)	0.0	8.7	23.6	35.9	50.2	61.6*
	Waves/s	14.1	20.9	17.7	13.2	7.5	4.0*
SU	Cm (μg/ml)	0.0	9.4	19.8	31.5	44.8*	—
	Waves/s	9.3	18.5	12.2	3.7	1.8*	—

Mean Cm from last 3 min and mean effect values from last 2 min at the end of each target concentration or earlier when burst suppression* occurred.

EEG = electroencephalogram; Cm = measured serum thiopental concentration.

Having demonstrated that blood:EEG effect site equilibration occurs within 3 min, we were able then examine the thiopental pseudo–steady-state serum concentration *versus* number of waves per second relationship in the last 3 min of each 6 min target concentration. By limiting each target concentration to only 6 min it was possible to obtain four to five constant serum concentrations within 24–30 min and to limit the dose of thiopental to a total of 1–2 g. This allowed us effectively to "step through" the therapeutic window of thiopental and define the serum concentration *versus* EEG effect relationship.

Figure 6 displays the constant serum thiopental concentration *versus* number of waves per second relationship obtained in this study. The biphasic nature is visible and creates challenges both in the clinical use of the EEG and pharmacodynamic modeling of this relationship. Figure 5 demonstrates that one can have 8–13 EEG waves/s both at baseline, awake and with serum thiopental concentrations of 20–40 μg/ml. Interpreting the EEG effect requires one to know if the activation peak is being "ascended or descended." If a moderate dose of thiopental is given as an iv bolus, the activation phase will occur so rapidly that it may not be evident before slowing of the EEG becomes predominant. Only when the EEG slowing is below the baseline, *i.e.*, 8–13 waves/s, does it become clear what thiopental concentrations might be present. A monophasic EEG parameter would have significantly greater utility than the biphasic parameter we present. We have not been able to identify such a parameter for the thiopental EEG to date. This is also the nature of the raw EEG signal: first activation and then depression.

The biphasic serum thiopental concentration *versus* EEG effect relationship also creates a challenge in pharmacodynamic data analysis. A monophasic drug plasma concentration *versus* drug effect relationship can be characterized by a sigmoid E_{max} pharmacodynamic model with four parameters: E_0, the baseline effect; E_{max}, the maximal drug effect; a slope term; and the Cp_{50}, the concentration

TABLE 4. Pharmacodynamic Characterization of the Biphasic Serum Thiopental Concentration *versus* Number of Waves per Second Relationship

Subject	Baseline EEG Effect (waves/s)	Total AUC (waves · μg/s · ml)	Percent Activated AUC	Cm at Centroid (μg/ml)	EEG Effect at Centroid (waves/s)	Cm at EEG Peak (μg/ml)	EEG Effect at Peak (waves/s)	Cm at Baseline Return (μg/ml)	Cm at 50% of Baseline (μg/ml)
AL	9.4	514.0	35.5	17.0	19.5	14.9	20.7	27.0	32.5
HO	12.1	615.0	18.5	21.2	17.6	17.5	19.7	27.3	36.7
DO	8.5	512.4	30.3	19.8	14.9	14.7	15.6	33.2	40.6
TU	9.9	733.8	24.9	24.9	13.4	11.5	18.7	42.7	54.8
PE	14.1	946.5	15.6	28.9	15.9	11.9	21.3	33.7	51.7
SU	9.3	443.5	30.3	18.7	13.2	9.5	18.5	23.5	30.0
Mean	10.6	627.5	25.8	21.8	15.8	13.3	19.1	31.2	41.0
Coefficient of variation (%)	18.4	27.1	27.0	18.5	14.2	19.9	9.7	20.0	22.7

EEG = electroencephalogram; AUC = area under the curve; Cm = measured serum thiopental concentration.

at 50% effect. A biphasic profile of drug concentration *versus* response can be seen as arising from the sum of two sigmoid E_{max} models.[20] One term in the model contributes the activation component, while the other term yields the inhibitory portion of the biphasic concentration *versus* response. If the Cp_{50}s are not sufficiently separated, a clear maximal activation will not be reflected in the data. The absence of a clear activation plateau prevents estimation of the E_{max} parameter for the activation component. If this parameter is not known, it is not possible to know the Cp_{50} for the activation. Although a line can be fit to biphasic data using two sigmoid E_{max} models, the estimation of these parameters is intrinsically unstable and the physiologic interpretation is speculative at best.[21]

With the above issue in mind, we used the nonparametric pharmacodynamic characterization approach displayed in figure 1 and proposed by Ebling *et al.*[18] Nine descriptors can be used to characterize the data in figure 6, using both the concentration *versus* EEG effect at defined events, *i.e.*, baseline, peak activation, passage through baseline with drug present, 50% below baseline, or specific events defined from the area under the concentration–effect curve. The pharmacodynamic descriptors we have used for thiopental can be used to statistically compare different groups of patients or different drugs that cause similar EEG drug effects. These descriptors can be used to compare the relative potency of different drugs.[18] However, the intuitive nature of a biphasic drug effect is much more complex relative to monophasic concentration–response functions and parameters like the Cp_{50}. The only pharmacodynamic parameter that was not well characterized in our study was the thiopental concentrations that caused maximal slowing or 0 waves/s. A target thiopental concentration greater than 50 μg/ml would have been necessary to obtain a continuously isoelectric EEG and more accurately define the concentrations at this EEG endpoint. We could not justify the larger doses and possible risk of hemodynamic depression to gather these data.

Our previous pharmacodynamic modeling of the thiopental's effects on the EEG used the serum thiopental concentration *versus* spectral edge relationship[3–5] and a single, monophasic, sigmoid E_{max} pharmacodynamic model. In these studies we did not pharmacodynamically characterize the EEG activation phase. The E_0 of the pharmacodynamic model was the maximal EEG activation seen. The E_{max} in the pharmacodynamic model was the lowest spectral edge value measured in the experiment. Because the FFT waveform analysis and spectral edge parameter cannot characterize isoelectric EEG, we carefully infused thiopental until early burst suppression occurred to prevent the spectral edge parameter from becoming unstable. The Cp_{50} obtained from this previous pharmacodynamic modeling approach was approximately 20 μg/ml.[3–5] By using the number of waves per second from aperiodic waveform analysis, it becomes possible to characterize a deeper stage of thiopental anesthesia, that associated with isoelectric EEG, which is not possible using the spectral edge and FFT waveform analysis. This deeper level may be very relevant to the correlation of clinical depth of anesthesia to the EEG. Also, the current study design using the CCIP allows for reasonable characterization of the EEG activation phase. The current study has resulted in a more complete characterization of the serum thiopental concentration *versus* EEG response relationship compared to our previous research with the spectral edge EEG measurement.

In summary, we used a CCIP to achieve pseudo–steady-state serum thiopental concentrations that "step through" the therapeutic window of thiopental's concentration *versus* EEG effect. The biophase or effect site, as monitored by the EEG, equilibrated rapidly, within 2–3 min, and thereafter remained stable. Using the number of waves per second parameter from aperiodic waveform analysis, it was possible to characterize the effects of thiopental on the EEG, including the activation at low serum thiopental concentrations and burst suppression at high thiopental concentrations. A distinct, biphasic serum thiopental concentration *versus* EEG response relationship has been established. The methodology developed should have significant utility in defining the relationship between thiopental's clinical depth of anesthesia and the EEG.

Appendix: Evaluating EEG Parameters to Measure Thiopental CNS Drug Effect

In order to use the EEG signal as a measure of drug effect on the CNS, the complex, unprocessed EEG has to be reduced to a specific "effect parameter" that allows numerical quantitation. Two waveform analyses have been used to quantitate thiopental's effect on the EEG: the FFT and aperiodic analysis.

The goal of this study was to find an EEG measure of thiopental effect that met the following criteria:

1. Summarize the changes of EEG morphology in numerical values
2. Be stable at baseline
3. Be consistent with the most prominent drug-induced property visible in the raw EEG tracing with a minimal amount of data transformation
4. Show both onset and recovery of the EEG effect in relation to serum drug concentrations with some degree of hysteresis or time lag relative to arterial blood concentrations.
5. Be obtainable using readily available hardware and software.

The above criteria are based on general principles of clinical pharmacology that can be applied to most measures of drug effect.[22]

Institutional human use approval and informed consent were obtained to study six healthy male subjects (age 25–39 yr, weight 62–99 kg). After 5 min of baseline EEG, thiopental was infused at a rate of 100 mg/min. The infusion was stopped 0.5–1 min after intervals of 3 s of isoelectric EEG had been noted. Venti-

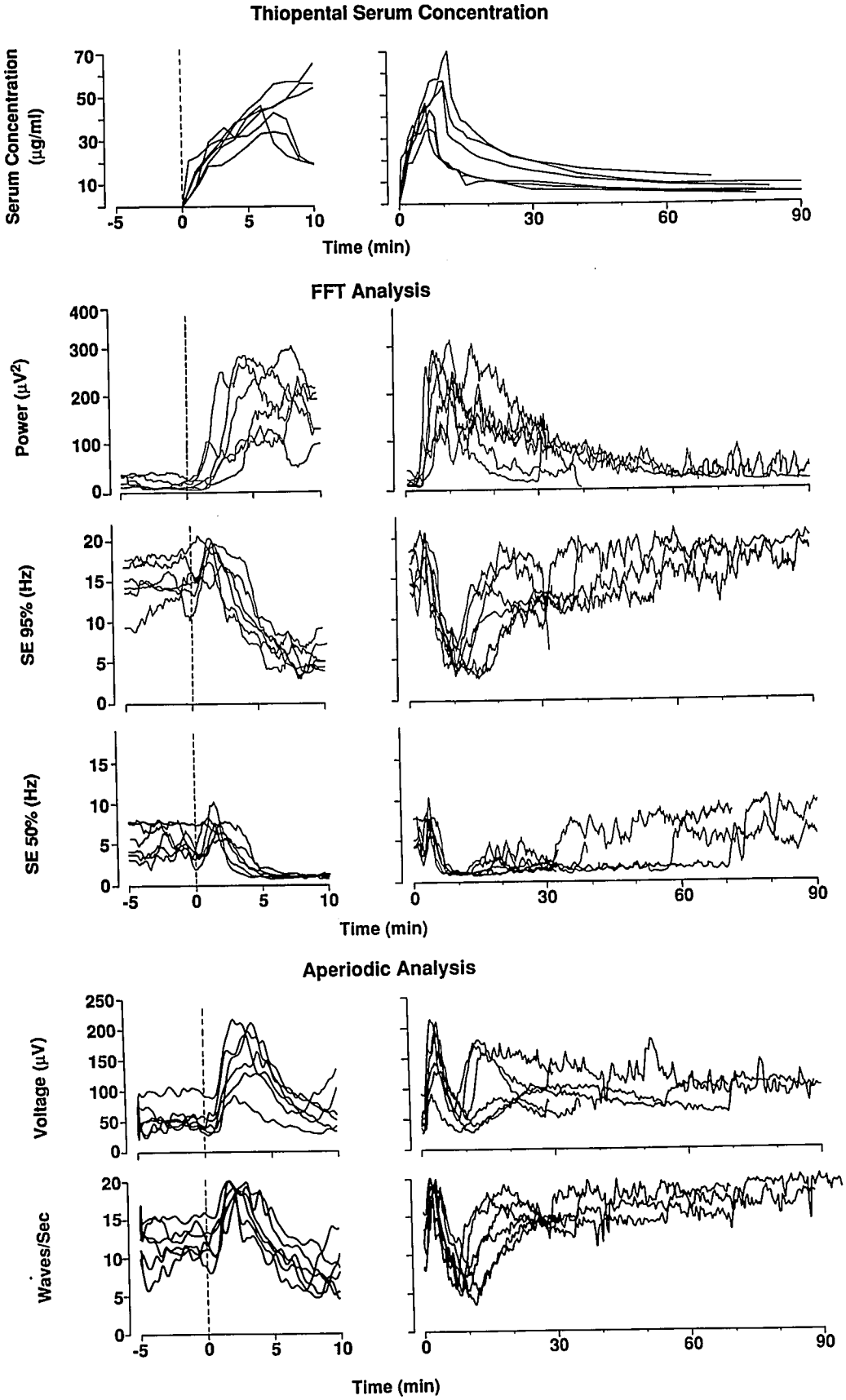

FIG. 7. A summary of the derived EEG parameters calculated from lead Fp1-O1 in six subjects. After recording of the EEG baseline, infusion of thiopental (100 mg/min) was initiated at time zero (dashed line, *left*) and terminated 0.5–1 min after the occurrence of 3 s of burst suppression in the EEG, resulting in administered doses of 600–1,100 mg. The corresponding serum concentrations are displayed in the left top panel for the first 10 min and in the right top panel for the entire time of the experiment (60–90 min). *Center:* Parameters derived from fast Fourier transform (total power, spectral edge 95% and spectral edge 50%). *Bottom*: Parameters derived from a periodic analysis (total number of waves per second and total voltage per second).

lation was assisted as clinically indicated, and arterial P_{CO_2} was periodically measured. Arterial samples were obtained for determination of serum thiopental levels.

In principle, an infinite number of univariate EEG parameters could be derived from waveform analysis. We chose to examine three parameters from the FFT analysis and two parameters from the aperiodic analysis. From the FFT analysis, we calculated: spectral edge frequency 95% (SE95%), median power frequency (SE50%), and total power. SE95% or SE50% represents the frequency below which 95% or 50%, respectively, of the power is located. From the aperiodic analysis we calculated the total number of waves per second and total voltage per second derived from 1–30 Hz at 1-s intervals. We visually examined the EEG effect *versus* time and thiopental concentration *versus* time curves relative to the pharmacologic criteria previously proposed.

Figure 7 summarizes the overall performance of the derived EEG parameters in the 6 subjects during the thiopental infusion and after the infusion was terminated. The measured serum thiopental concentrations *versus* time are displayed. The dashed line in the left panel indicates the start of thiopental infusion. Because the infusion was continued to a defined EEG endpoint (3 s of isoelectric EEG), the time of infusion varied with each subject.

When the behavior of the parameters that summarize the events from baseline until burst suppression (fig. 7) is examined, it is evident that the power parameter from FFT analysis does not follow the biphasic pattern visible in the raw EEG tracing. SE95% does not consistently characterize the activation but tracks slowing in the raw EEG. SE50% does not discriminate baseline from activation and is not sensitive to drug effect until shortly before the appearance of burst suppression. The total voltage/s parameter from aperiodic analysis does not discriminate baseline from the EEG effect observed at burst suppression. The number of waves per second parameter from aperiodic analysis, however, summarizes and characterizes the biphasic pattern of drug effect in the raw EEG tracing in all subjects.

For the characterization of the recovery of effect (fig. 7), the SE95% and number of waves per second parameters demonstrate that the EEG is returning to a state of activation at the time serum thiopental concentration is decreasing. We did not record the EEG long enough to allow the signal to return to the true awake baseline.

Figure 7 demonstrates that number of waves per second from aperiodic analysis and, to a lesser extent, SE95% from FFT analysis quantitate the events that are obvious in the raw EEG tracing: baseline, stages of EEG activation and slowing, and recovery from thiopental drug effect. In a previous study we have shown that these derived parameters (SE95% and number of waves per second) are stable at least for 4 h in the absence of any drug.[22] A limitation of the SE95% is the less than ideal quantitation of the initial activation phase and the inability to characterize isoelectric EEG, a characteristic of deep thiopental hypnosis. FFT analysis becomes unstable when isoelectric EEG patterns occur and the total EEG power markedly decreases. Although SE95% and number of waves per second originate from fundamentally different concepts of waveform analysis and although they represent different aspects of the waveform, they manifest similarity in the drug effect *versus* time curves. This consistency will allow one to use either the number of waves per second parameter from aperiodic analysis or SE95% from FFT as a measure of continuous, noninvasive thiopental CNS drug effect. FFT analysis assumes that the EEG signal is a continuous periodic waveform that is composed from multiple sinusoidal signals. This technique behaves well with continuous signals but is difficult to interpret during periods of random burst suppression. Unlike FFT analysis, aperiodic analysis does not assume periodicity in the EEG signal. Aperiodic analysis is consistent with a stochastic view of EEG signal propagation. It quantitates the wavelength (duration) and amplitude (voltage) of each EEG event (wave). Because it does not rely on a periodic view of EEG propagation it can handle continuous as well as discontinuous EEG signals robustly.

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