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A Model for Studying Depth of Anesthesia and Acute Tolerance to Thiopental

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Using power spectral analysis of the electroencephalogram (EEG) to measure the effect of thiopental on the brain, the authors investigated the phenomenon of acute tolerance. Three sequential infusions of thiopental, 20–25 min apart, were given to eight healthy volunteers. The infusions were stopped when moderately deep anesthesia, indicated by burst-suppression on the EEG, was reached. The mean (±SD) doses of thiopental for the first, second, and third infusions were 9.6 ± 2.0, 5.6 ± 0.9, and 5.2 ± 1.2 mg·kg^{-1}, respectively. The spectral edge (Hz), defined as the frequency below which 95% of the total EEG power is located, was used to measure thiopental effect. A pharmacodynamic model was used to quantify the relationship of the plasma concentration of thiopental to its effect on the spectral edge. The model estimates the baseline spectral edge, E_o (Hz), the maximal decrease of the spectral edge due to thiopental, E_{max} (Hz), and the thiopental serum concentration required to produce 50% of the maximal shift of the spectral edge, the IC_{50} (μg·ml^{-1}). The IC_{50} is an index of brain sensitivity to thiopental. If acute tolerance to thiopental had developed, the IC_{50} of the second and third infusions would have been greater than the IC_{50} of the first infusion. However, there were no significant differences between the values of the IC_{50} of each infusion (15.9 ± 5.1, 13.9 ± 3.4, and 16.0 ± 4.4 μg·ml^{-1} respectively), indicating that acute tolerance did not develop during repeated infusions of thiopental. The values for E_o and E_{max} also did not change significantly, providing additional evidence that the concentration-effect relationship remained constant. The combination of power spectral analysis of the EEG with pharmacodynamic modeling may prove to be a powerful tool for studying the clinical pharmacology of intravenous anesthetics. (Key words: Anesthetics, intravenous: thiopental. Monitoring: electroencephalogram. Pharmacology: pharmacodynamics. Tolerance: acute.)

THE CLASSICAL METHOD of studying the potency of an intravenous anesthetic is to conduct a dose–response study. There are several disadvantages to this technique. The relationship between dose and response can be very distant, and it is affected by two groups of factors. Dose–response curves are influenced by the relationship of dose to the resulting plasma concentration, or pharmacokinetics, and by pharmacodynamics, the relationship between concentration and response. If a dose–response relationship changes, one does not know whether this was due to altered pharmacokinetics, pharmacodynamics, or both. As well, the ED_{50} obtained from single-dose studies is a population estimate and cannot predict individual dose requirements. Because of these limitations, we tried to characterize the relationship between the plasma concentration of thiopental and the resulting effect on the brain. The second objective of our study was the estimation of brain sensitivity to thiopental in individual subjects.

Investigation of concentration–response relationships requires a precise measure of drug effect. Thiopental produces a characteristic progression of electroencephalographic changes,[1] so that the EEG can be used to measure the effect of thiopental on the brain (fig. 1). As the patient loses consciousness, there is an increase in frequency and a slight increase of amplitude (stage 1, fig. 1). The second stage is characterized by a further increase of amplitude accompanied by marked slowing of the frequency. Stage 3 is characterized by bursts of electrical activity interspersed with relatively isoelectric periods. This pattern is referred to as burst-suppression. Studies in the 1950s concluded that stages 2 and 3 represent surgical anesthesia.[1,2] Through stage 4 there is progressive prolongation of the isoelectric periods until stage 5, a continuously isoelectric EEG, ensues. We used power spectral analysis[3] of the EEG as a measure of thiopental effect. We then were able to quantify the relationship between the serum concentration of thiopental and its effect on the brain by pharmacodynamic modeling.[4]

In 1951, Brodie *et al.*[5] reported that subjects given larger doses of thiopental had higher plasma thiopental concentrations at the time of awakening. The clinical importance of this observation was uncertain because

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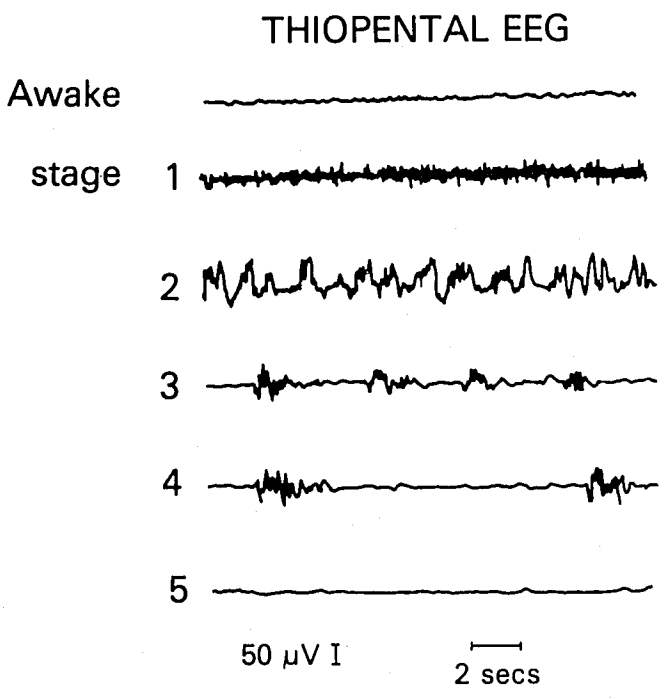

FIG. 1. The electroencephalographic changes induced by thiopental. Consciousness is lost early in stage 1. Stages 2 and 3 represent surgical anesthesia.[1,2] Barbiturate coma is indicated by stages 4 and 5.

of the very large doses used (22–67 $mg \cdot kg^{-1}$). Dundee *et al.*[6,7] subsequently reported this phenomenon in patients given lower doses of thiopental (up to 15 $mg \cdot kg^{-1}$). Brodie, Dundee, and their colleagues attributed their findings to the rapid development of tolerance to thiopental.[5–7] In this report, we describe a new method of estimating brain sensitivity to thiopental, and we have used it to determine if acute tolerance developed with repeated doses of thiopental.

Methods

Experimental Protocol

After approval by the Human Studies Committee, informed consent was obtained from eight healthy men. Following an overnight fast, the volunteers had intravenous catheters placed in opposite arms for thiopental administration and blood sampling. A precordial stethoscope and ECG leads were applied and an automatic blood pressure cuff (Dinamap®) was placed around the calf.

After several minutes of baseline EEG were recorded, all subjects were given three sequential thiopental infusions. The infusion rate for subjects 1–4 (Group 1) was 150 mg/min; for subjects 5–8 (Group 2), it was 75 mg/min. The infusion was stopped when the EEG showed burst-suppression (stage 3, fig. 1). Recovery to a light plane of anesthesia (stage 1, fig. 1), which required 20–25 min, was allowed. The second infusion then was begun and again stopped when burst-suppression appeared. The third infusion was given in an identical fashion.

Blood samples for thiopental analysis were drawn through catheters placed into the axillary vein via the basilic vein. Samples were drawn at intervals of 0.5–1 min during the infusions and at intervals of 1 to 2 min between infusions. Sampling was continued at 3-h intervals for 24 h. Venous blood gases were drawn at the end of each infusion.

Analytic Techniques

Total serum thiopental concentrations (protein-bound and free drug) were measured with a high-performance liquid chromatography assay[8] sensitive to 10 $ng \cdot ml^{-1}$. The coefficient of variation of the assay was 2.9% at 5 $\mu g \cdot ml^{-1}$. The free (unbound) fraction of thiopental for each subject was determined by ultrafiltration of serum samples containing 10 and 30 $\mu g \cdot ml^{-1}$ thiopental.[9] These concentrations were selected because they were representative of the peak and trough levels resulting from the infusions.

EEG Signal Processing

The EEG signals from the anterior and posterior halves of each hemisphere were amplified by a Beckman Accutrace® EEG machine and were recorded on magnetic tape using an 8-channel FM recorder (Vetter Model A). Because the signal was similar in all leads, the left fronto-central lead was chosen arbitrarily for processing by a PDP 11/40 computer (Digital Equipment Corporation). After digitization of the EEG signal, Fourier analyses of consecutive 4-s periods were computed. The Fourier transformation breaks down the EEG waveform into its frequency and amplitude components. The power, which is the square of the amplitude, then can be quantified at any given frequency. From this information, a power *versus* frequency histogram can be constructed for each 4-s epoch.[3]

The spectral edge[10], defined as the frequency below which 95% of the EEG power is located, was derived from the power *versus* frequency histogram of each epoch (fig. 2). The spectral edge provides an essentially continuous index of cerebral electrical activity and may be thought of as the highest frequency at which there is significant power.

Data Analysis

To determine whether the site of action of thiopental was within the central (plasma) compartment, the spec-

tral edge *versus* plasma thiopental concentration data were examined for hysteresis.[11] This is accomplished by comparing the area under the spectral edge *versus* concentration curve during the infusion (when the concentration is increasing) with the area under the curve when the concentration is decreasing (after the infusion). The areas are calculated by the linear trapezoidal rule. If the areas are different, the relationship of concentration to spectral edge exhibits hysteresis. The presence of hysteresis would indicate that the site of action of thiopental is kinetically distinguishable from the plasma compartment and that there is a distinct time lag between changes in plasma concentration and changes in response. Intuitively, this would mean that the site of action was some "distance" from the plasma.

The decrease of the spectral edge between stage 1 and stage 3 was related to the plasma concentration of thiopental by the following sigmoid inhibitory E_{max} pharmacodynamic model[4]:

$$\text{Spectral edge} = E_o - \frac{E_{max} \times Cp^{\gamma}}{IC_{50}^{\gamma} + Cp^{\gamma}}$$

This equation states that the spectral edge (Hz) is equal to its baseline value, E_o (Hz), minus a term describing the decrease of spectral edge with increasing thiopental concentration. Cp is the thiopental serum concentration while γ is a power function that determines the steepness of the concentration–response curve. E_{max} (Hz) is the maximal decrease of spectral edge caused by thiopental. The denominator is the IC_{50} plus the serum concentration, both raised to the same power. The IC_{50} is the thiopental serum concentration ($\mu g \cdot ml^{-1}$) causing half the maximal spectral edge shift. It is an index of brain sensitivity to thiopental based upon the EEG changes induced by thiopental.

The spectral edge *versus* concentration data were entered into a computer, so that the variables E_o, E_{max}, γ, and IC_{50} could be estimated by nonlinear regression.¶ The concentration entered was the total (bound + free) thiopental serum concentration. The IC_{50} based upon free, unbound thiopental was calculated by multiplying the IC_{50} based upon total thiopental concentration by the unbound fraction. To investigate the phenomenon of acute tolerance, all pharmacodynamic variables were estimated for each of the three infusions independently.

Student's *t* test for unpaired data was used to analyze the demographic and hemodynamic data. The paired *t* test was used to compare the areas of the spectral-edge–concentration curves. Repeated measures analysis of variance was used for the pharmacodynamic data. Values of $P < 0.05$ were considered statistically significant.

¶ Nichols AL, Peck CC: LSNLR—General weighted least squares non-linear regression program. Technical Report No. 5, Division of Clinical Pharmacology, Uniformed Services University for the Health Sciences, Bethesda, Maryland, May 1981.

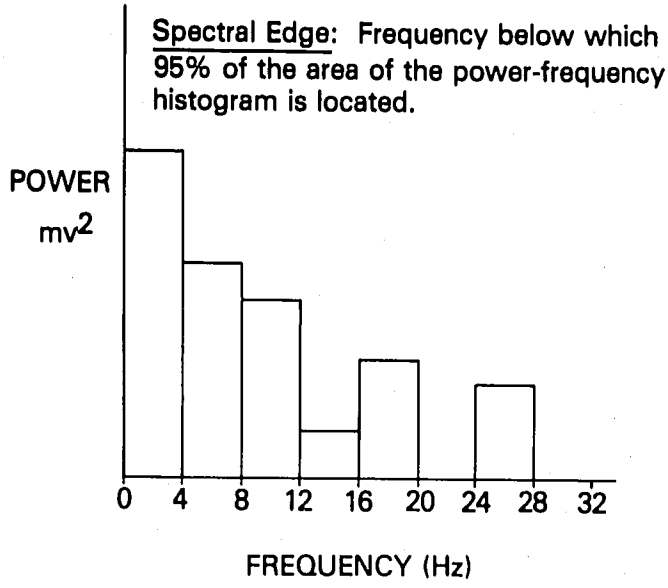

FIG. 2. A schematic of a power versus frequency histogram for a hypothetical 4-s epoch. In this example, the spectral edge would be 26 Hz.

Results

The two groups of subjects were comparable in age, weight, and the doses of thiopental they received (table 1). As would be expected, the dose given during the second and third infusion was lower than the first infusion, because of thiopental remaining in the body from the preceding infusions. The total dose of the first infusion was slightly, but not significantly, higher in those subjects receiving thiopental at 75 $mg \cdot min^{-1}$. This slight difference was expected, because the slower infusion rate allows more time for redistribution of thiopental from the brain to other tissues. The results from the two groups have been pooled because they did not differ statistically.

The mean arterial pressure decreased from an average control value of 83 ± 11 (SD) mmHg to 61 ± 10 mmHg at the end of the infusions. This was accompanied by an increase in heart rate from 65 ± 9 to 96 ± 11 beats $\cdot min^{-1}$. Assisted mask ventilation occasionally was necessary for 60–90 s at the deepest levels of anesthesia. Venous blood *p*H and P_{CO_2} always were within normal limits at the end of each infusion.

The infusion protocol for one subject and the resulting changes in plasma thiopental concentration and spectral edge are shown in figure 3. Thiopental produces progressive slowing of the EEG, so that the spectral edge moves to a lower frequency with increasing

TABLE 1. Subject Data (Mean ± SD)

	Age (yr)	Weight (kg)	Thiopental Dose (mg/kg)		
			1st Infusion	2nd Infusion	3rd Infusion
Group 1	26.0 ± 5.8	74.9 ± 8.0	8.4 ± 1.3*	5.7 ± 0.4	5.7 ± 1.6
Group 2	34.5 ± 5.9	78.2 ± 8.2	10.7 ± 2.1*	5.6 ± 1.3	4.7 ± 0.5
All	30.3 ± 7.1	76.7 ± 7.7	9.6 ± 2.0*	5.6 ± 0.9	5.2 ± 1.2

* $P < 0.05$ for first *versus* third infusions.

thiopental concentrations. The obvious tracking of the fluctuations in thiopental concentration by the spectral edge suggests that equilibration of thiopental between plasma and its sites of action is very rapid. The figure also demonstrates that the rate of recovery of the spectral edge and the degree of recovery progressively decreases with each infusion. This is because of the progressive accumulation of drug in plasma and in brain tissue. The spectral edge tracing has the same shape that a brain thiopental concentration curve theoretically would have.

The mean (±SD) area under the spectral edge *versus* concentration curves when the concentration was increasing was 345 ± 158 $Hz \cdot \mu g \cdot ml^{-1}$. When the concentration was falling, the mean area was 332 ± 145 $Hz \cdot \mu g \cdot ml^{-1}$. This difference is not significant ($P = 0.77$). This absence of hysteresis indicates that thiopental equilibrates between blood and brain virtually instantaneously.

Plotting spectral edge against concentration reveals the sigmoid nature of their relationship. Figure 4 shows the data from the first infusion in one subject. The solid line is the spectral-edge–concentration curve predicted by the pharmacodynamic model, which closely approximates the actual data. The estimates of the pharmacodynamic variables are given in table 2. Examining the results for the first infusion shows the mean (±SD) E_o to be 24.5 ± 4.2 Hz. This value represents the spectral edge during EEG stage 1 (fig. 2) thiopental anesthesia. The decrease of the spectral edge between stages 1 and 3, E_{max}, was 13.7 ± 2.4 Hz. The mean IC_{50} for the first infusion was 15.9 ± 5.1 $\mu g \cdot ml^{-1}$.

The predicted spectral edge *versus* concentration curves for all three infusions in the same subject are shown in figure 5. If tolerance were developing to the effect of thiopental on the spectral edge, the curves for the second and third infusions would lie to the right of the curve for the first infusion, and this would increase

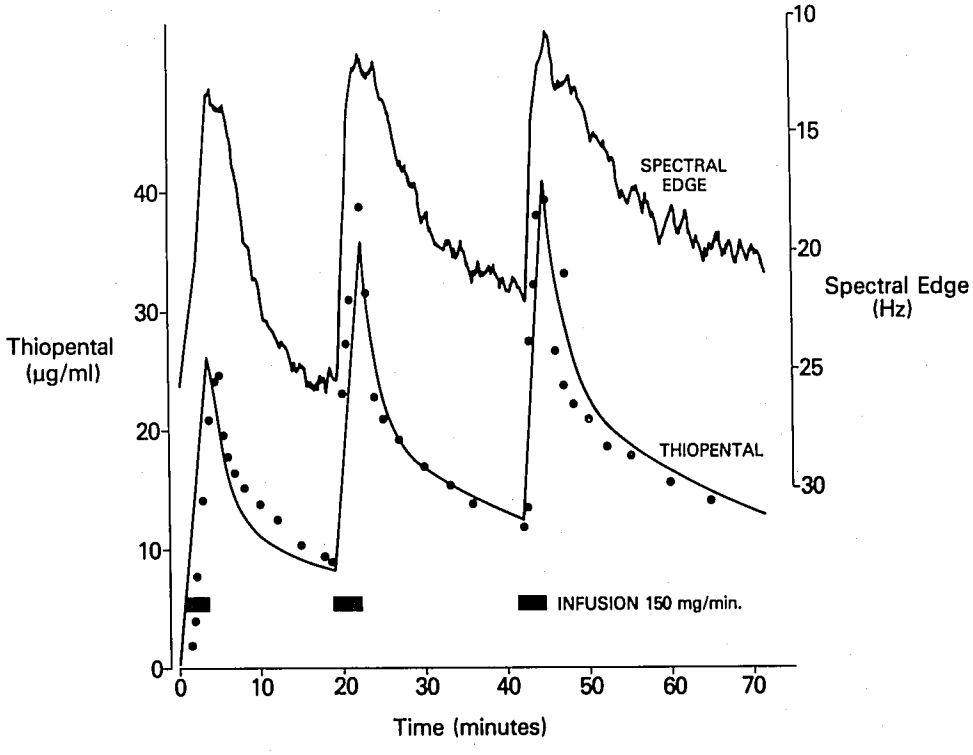

FIG. 3. The experimental data from one subject. The horizontal bars indicate the timing and duration of the thiopental infusions. The dots are the measured thiopental serum concentration ($\mu g \cdot ml^{-1}$) and the line adjacent to them shows the fit of a two-compartment pharmacokinetic model to the concentration versus time data. The spectral edge (Hz) tracing is shown above the thiopental concentration. Because the spectral edge moves to a lower frequency with increasing thiopental concentration, the spectral edge scale has been inverted for visual clarity.

the IC_{50}. Comparison of the first, second, and third infusions reveals no statistically significant ($P < 0.05$) change in the IC_{50} (table 2). The estimates of E_o and E_{max} also were unchanged (table 2), providing additional evidence that the concentration–response relationship remained constant.

The free fraction of thiopental at 10 μg/ml was within 2% of the free fraction at 30 μg/ml, so the mean of these two values for each patient is given in table 2. The range of the values of the free fraction is very narrow. Comparison of the free IC_{50} (the product of the free fraction and the IC_{50}) of the three infusions reveals no significant differences. The average coefficients of variation (SD/mean × 100%) for the IC_{50} based upon total thiopental concentration and the IC_{50} based on the free thiopental concentration were 28% and 24%, respectively. This indicates that the variability in responsiveness to thiopental is due to variability in central nervous system (CNS) sensitivity and not variations in the degree of thiopental serum protein binding.

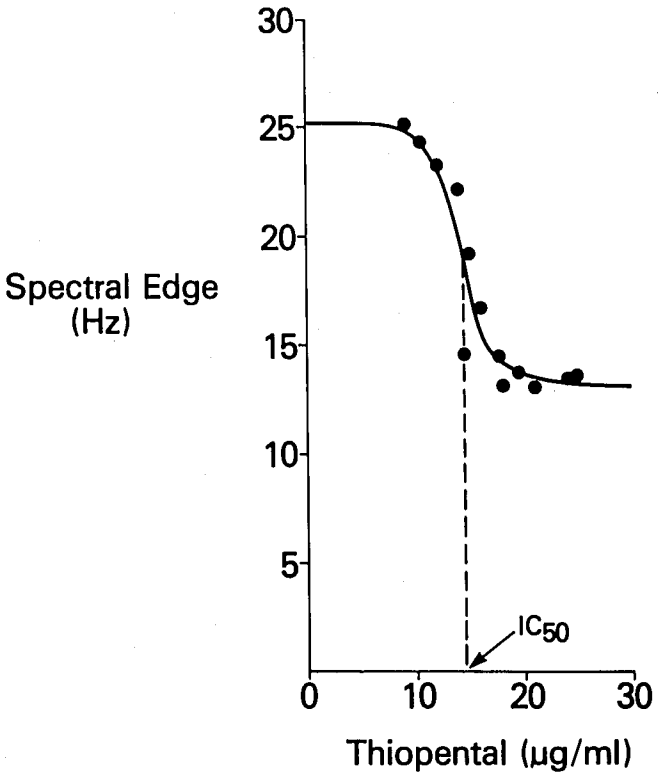

FIG. 4. The spectral edge versus concentration data for the first infusion in subject 3. The symbols are the actual data; the solid line is the effect-concentration curve predicted by the pharmacodynamic model.

Discussion

The time course of the change of the serum concentration of thiopental following an intravenous dose in healthy subjects has been reported by several investigators.[12–15] In contrast to this wealth of information about the pharmacokinetics of thiopental, there is a paucity of information regarding thiopental pharmacodynamics—the relationship of plasma concentration to drug effect. Becker[16] determined the arterial thiopental concentration required to abolish the corneal reflex and movement in response to squeezing the trapezius muscle in 50% of subjects (AD_{50}). These responses were shown to be well correlated with the presence or absence of movement in response to surgical stimulation.[16] Our approach differs from that of Becker in two important ways. We obtained a continuous measure of thiopental effect, the spectral edge, rather than testing drug effect at discrete intervals. The spectral edge data were used to characterize the entire concentration–response curve from light to moderately deep thiopental anesthesia. In contrast, Becker was able to quantify only a single point of the concentration–response curve, the AD_{50}. Brand and colleagues[17] unsuccessfully tried to correlate thiopental plasma concentration with drug-induced EEG

TABLE 2. Pharmacodynamic Parameters Independently Determined for the First, Second, and Third Infusions

E_o (Hz)				E_{max} (Hz)				IC_{50} (μg/ml total thiopental				
	1st Infusion	2nd Infusion	3rd Infusion		1st Infusion	2nd Infusion	3rd Infusion		1st Infusion	2nd Infusion	3rd Infusion	Thiopental Free Fraction
Subject				Subject				Subject				
1	25.9	23.5	21.7	1	9.0	7.0	4.6	1	16.9	19.3	22.4	0.12
2	23.1	24.8	23.2	2	7.6	11.7	10.5	2	13.6	13.4	14.0	0.14
3	25.3	28.0	26.3	3	12.1	16.7	15.0	3	14.2	14.8	14.8	0.13
4	32.3	26.6	28.1	4	18.6	14.6	15.1	4	10.9	11.7	12.3	0.14
5	25.2	28.3	23.8	5	15.1	18.9	15.0	5	18.0	8.3	10.7	0.13
6	23.2	22.8	17.6	6	16.1	17.4	10.7	6	11.8	11.8	13.3	0.13
7	17.1	17.9	15.1	7	8.3	11.1	7.5	7	15.1	16.1	19.3	0.13
8	24.0	30.2	24.3	8	22.8	26.2	24.3	8	27.1	15.9	21.1	0.12
Mean	24.5	25.3	22.5	Mean	13.7	15.4	12.8	Mean	15.9	13.9	16.0	0.13
SD	4.2	3.9	4.3	SD.	2.4	5.8	6.0	SD	5.1	3.4	4.4	0.01

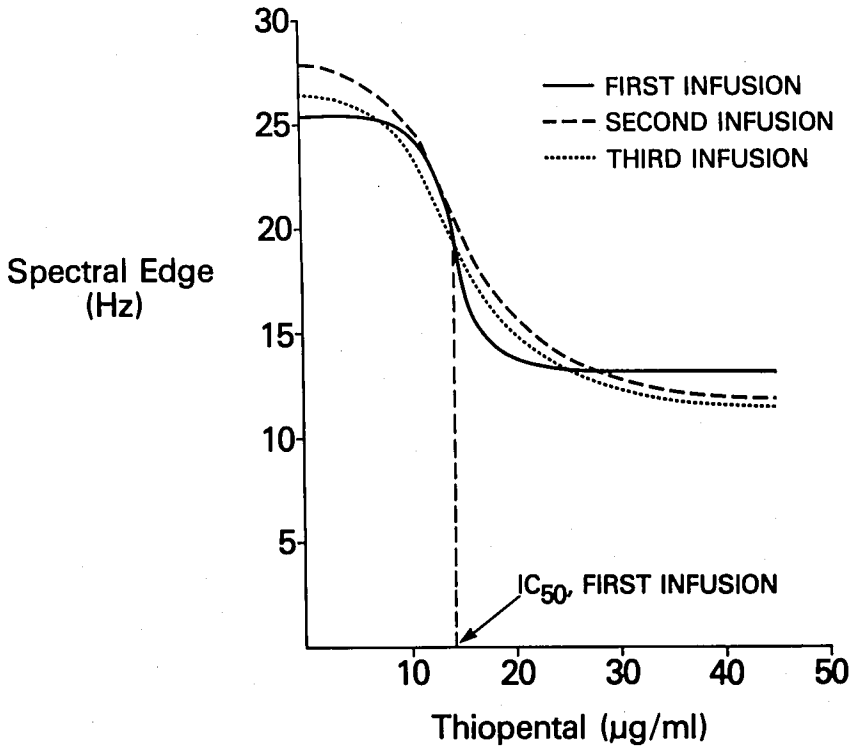

FIG. 5. The spectral-edge–concentration curves for all three infusions in subject 3. The virtual superimposition of these curves indicates that tolerance to the effect of thiopental on the spectral edge did not develop during the course of the study.

changes. They inspected the EEG tracings visually and classified them according to Kiersey *et al.*[1] (fig. 1). We have overcome the difficulties encountered by Brand *et al.* by using computer-assisted EEG processing, a sigmoid relationship between concentration and effect, and allowing for intersubject variability. The overall slowing seen on our unprocessed EEG tracings was reflected accurately by the spectral edge, which moved to a lower frequency. As our results indicate, the relationship between thiopental concentration and EEG changes indeed can be quantified precisely.

It is important to emphasize that we modeled only one portion of the EEG response to thiopental. We were unable to characterize the transition from the awake EEG pattern to the high-frequency, low-amplitude pattern of light thiopental anesthesia (stage 1, fig. 1). Both this transition and the duration of stage 1 were very brief, so that there were simply not enough data for pharmacodynamic modeling. To avoid severe cardiac and respiratory depression, we did not study the transition from moderately deep anesthesia (stage 3) to profound depths of anesthesia indicated by an isoelectric EEG (stage 5). Because we modeled only the transition from stage 1 to stage 3 and back to stage 1, the baseline effect, E_o, actually represents the spectral edge of the early high-frequency, low-amplitude stage of thiopental anesthesia. The maximal shift of the spectral edge, E_{max}, represents the shift between phase 1 and phase 3. The power function, γ, influences the shape of the sigmoid curve. Its value generally was greater than 3, indicating a steep concentration–effect curve. Inhalation anesthetics[18] and narcotics[19] also have steep concentration–effect curves.

The last parameter of the model, the IC_{50}, quantifies brain sensitivity to thiopental. It is defined precisely as the serum concentration of thiopental causing 50% of the maximum shift of the spectral edge during transition from light (EEG stage 1) to moderately deep (stage 3) thiopental anesthesia. The IC_{50} can be expressed as either total thiopental concentration or the concentration of free drug. The IC_{50} is somewhat analogous to the minimum alveolar concentration (MAC)[20] for inhalational anesthetics and to Becker's AD_{50} for thiopental. All are indices of brain sensitivity to anesthetic drugs and relate concentration, rather than dose, to effect. However, the IC_{50} is derived from a continuous pharmacologic response, while MAC and the AD_{50} are determined by the presence or absence of movement after a noxious stimulus.

The pharmacodynamic model we chose, though complex, has several advantages over simpler models. The effect *versus* concentration curve has a sigmoid shape, which is characteristic of many physiologic and pharmacologic responses. A sigmoid function allows for a threshold concentration, below which there is little or no effect. A very simple pharmacodynamic model, such as a linear relationship between concentration and effect, does not allow for a threshold concentration nor a maximal response. The sigmoid function is the sim-

plest model that can characterize the data adequately and consistently.

Our thiopental-concentration–spectral-edge data were examined for the presence of hysteresis, which could not be demonstrated consistently. Changes of serum thiopental concentration are tracked very closely by the spectral edge, providing additional evidence that thiopental equilibrates exceedingly rapidly. If hysteresis were present, response at any given serum concentration would vary, depending on whether the concentration was increasing or decreasing.[4] Because thiopental equilibrates virtually instantaneously, the measured serum concentrations can be related directly to drug effect without attaining steady state. This technique is advantageous because of its simplicity. However, it does require that blood samples for drug analysis be drawn at frequent intervals so that enough concentration–spectral-edge data are available for analysis.

The absence of hysteresis may result in part from venous blood sampling. Had arterial sampling been used, the arteriovenous concentration difference would have been exaggerated during the infusion, and the spectral-edge–concentration curve would have shifted to the right while the concentration was increasing. Our failure to demonstrate significant hysteresis does not invalidate our results. It means only that the time course of changes in axillary venous thiopental concentration is indistinguishable from the time course of changes of the EEG response to thiopental. A corollary is that changes of axillary venous concentration approximate changes of thiopental concentration in cerebral venous effluent.

Brodie *et al.*[5] and Dundee and colleagues[6,7] have suggested that tolerance to thiopental develops rapidly. Acute tolerance implies that exposure of the brain to an initial dose of thiopental renders it less sensitive to subsequent doses. The sequential infusion design of our study allowed us to investigate this phenomenon. If tolerance were developing to the effect of thiopental on the sepectral edge, the IC_{50} of the second and third infusions would be greater than the IC_{50} of the first infusion. However, the IC_{50} remained essentially constant. Furthermore, the estimates of E_o and E_{max} also were not changed significantly, confirming that the concentration–response relationship remained constant. These results indicate that tolerance to the effects of thiopental on the EEG did not develop within the hour-long duration of our studies.

We can only speculate on the reasons for the difference between our results and those of other investigators. They studied the transition from light anesthesia to consciousness, while we examined the transition from light to moderately deep anesthesia. It has been suggested that acute tolerance is quantitatively greater at very light levels of thiopental anesthesia,[21] compared with the deeper stages that we studied. Also, although the results of Dundee *et al.* are statistically significant, their data demonstrate considerable variability.[6,7] The time of awakening could be thought of as being on the initial flat portion of a sigmoid response *versus* concentration curve. This results in considerable variation in concentration with little change of response. This variability could be compounded by using an imprecise measure of drug effect such as the presence or absence of response to a verbal stimulus. Obviously, the intensity of the stimulus will affect the response, so that this may not be as sensitive a means of measuring thiopental effect as continuous monitoring of the EEG.

The finding of an unchanging relationship between barbiturate blood levels and the EEG during fairly deep anesthesia is not without precedent. Gronert *et al.*[22] showed in dogs that the pentobarbital blood concentration and the EEG did not change during continuous infusions for periods as long as 24 h. Thus, it may be that the EEG is an inherently more stable index of barbiturate-induced central nervous system depression.

The pharmacodynamic model we have described can be applied to other questions about thiopental anesthesia. Clinical experience has shown that the dose of thiopental must be adjusted for certain physiologic and pathologic states, such as advanced age, renal failure, and chronic alcoholism.[23] The concepts we have developed can be used to determine the role that altered brain sensitivity plays in altering dose requirements. The interactions of drug combinations and surgical stimulation and the relationship of anesthetic-induced EEG changes to clinical signs of anesthesia remain to be explored.

In summary, we have developed a pharmacodynamic model for thiopental anesthesia based upon power spectral analysis of the EEG. We have also found that equilibration of thiopental between the blood and its sites of action within the brain is exceedingly rapid. Our model was used to investigate the phenomenon of acute tolerance, which could not be demonstrated. Because other intravenous anesthetics and narcotics[24,25] also progressively slow the EEG, this model also should be able to characterize their concentration–effect relationships. An intriguing possibility is whether a given spectral edge during a balanced anesthetic represents a given depth of anesthesia, regardless of whether the primary agent is a barbiturate or a narcotic. If this were the case, monitoring of the spectral edge would provide a continuous noninvasive measure of the depth of anesthesia.

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