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Thiopental Pharmacodynamics

II. Quantitation of Clinical and Electroencephalographic Depth of Anesthesia

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This study examined the relationship among pseudo–steady-state (constant) serum thiopental concentrations, clinical anesthetic depth as assessed by several perioperative stimuli, and the electroencephalogram (EEG). Twenty-six ASA physical status 1 or 2 patients participated in the study. Two constant serum thiopental concentrations were maintained in each patient using a computer-controlled infusion pump. The first randomly assigned target serum concentration of 10–30 μg/ml was maintained for 5 min to allow serum:brain equilibration. Then the following stimuli were applied at 1-min intervals: verbal command, tetanic nerve stimulation, trapezius muscle squeeze, and laryngoscopy. A second, higher, randomly assigned target serum concentration of 40–90 μg/ml was then achieved and maintained by the computer-controlled infusion pump. The previously described stimuli were reapplied, after which laryngoscopy and intubation was performed. A positive response was recorded if purposeful extremity movement or coughing was observed. Using the quantal movement or cough response and the measured constant serum thiopental concentration, the probability of no movement to each stimulus was characterized using logistic regression. The serum thiopental concentrations that produced a 50% probability of no movement response for the clinical stimuli were as follows: 15.6 μg/ml for verbal command, 30.3 μg/ml for tetanic nerve stimulation, 39.8 μg/ml for trapezius muscle squeeze, 50.7 μg/ml for laryngoscopy, and 78.8 μg/ml for laryngoscopy followed by intubation. The EEG was analyzed using aperiodic waveform analysis to derive the number of waves per second. A biphasic relationship between constant serum thiopental concentration and the EEG number of waves per second was observed. Loss of responsiveness to verbal stimulation occurred when the EEG was activated at 15–18 waves/s. Marked EEG slowing and isoelectric EEG (1–3 waves/s) associated with high serum thiopental concentrations (> 50 μg/ml) were necessary to prevent movement response to profound noxious stimuli such as laryngoscopy and intubation. The biphasic thiopental concentration–EEG relationship and the isoelectric EEG at the high serum thiopental concentrations needed to prevent purposeful movement responses limit the utility of the EEG as a measure of anesthetic depth when thiopental is used alone. This study demonstrates a conceptual approach to quantitate the serum thiopental concentration *versus* clinical and EEG depth of anesthesia. (Key words: Anesthetic depth: thiopental. Anesthetics, intravenous: thiopental. Brain: electroencephalography. Pharmacodynamics: aperiodic waveform analysis; electroencephalography; thiopental.)

OVER THE PAST 30 yr the assessment of depth of anesthesia has been a constantly evolving topic, with the introduction of newer drugs with more specific pharmacologic actions.[1] In a recent editorial, Prys-Roberts reexamined this issue and stated that depth of anesthesia is difficult to define because anesthetists have approached the issue in terms of the drugs available to them rather than the patient's needs during surgery.[2] He believes that the noxious stimulations of anesthesia and surgery induce a variety of reflex responses that may be independently modified by anesthetic drugs to the benefit of the patient. Prys-Roberts focused his concept on the body's response to noxious stimuli that can be ablated and attenuated by specific anesthetic drugs.

Inhalational anesthetic depth has been classically characterized by the minimum alveolar concentration (MAC) concept as developed by Eger and associates.[3] The measurement of MAC has several important elements, including 1) a constant partial pressure of volatile anesthetic at the site of action before measurement of response, 2) the application of a specific, noxious stimuli (initial skin incision in humans, tail clamping in animals), and 3) requirement for observation of a defined clinical response, usually purposeful movement. Our understanding of the pharmacology of inhalational anesthetics has been significantly enhanced with the determination of MAC.[4]

Unfortunately, similar unifying methodology or concepts to assess drug concentration *versus* depth of anesthesia have not evolved for the intravenous (iv) anesthetics such as thiopental, methohexital, or propofol. The traditional clinical use of intermittent, bolus iv administration of these drugs results in rapidly changing drug concentrations that preclude constant concentrations in the serum and at the site of action (biophase) during the application of clinical stimuli. We have demonstrated that a computer-controlled infusion pump (CCIP) can be used to attain rapidly and then maintain pseudo–steady-state (constant) serum thiopental concentrations.[5] These constant serum concentrations result in a constant intensity

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of drug effect as measured with the electroencephalogram (EEG) using the number of waves per second obtained from aperiodic waveform analysis.

The objectives of this study were 1) to determine the relationship of a constant serum thiopental concentration and the clinical anesthetic depth as assessed by several relevant clinical noxious stimuli and the purposeful movement response and 2) to correlate the thiopental EEG drug effect as measured by the number of waves per second derived from aperiodic waveform analysis with the clinical depth of anesthesia.

Materials and Methods

After obtaining institutional approval and individual informed consent, 26 healthy ASA physical status 1 or 2 male surgical patients participated in the study. All of the patients were free of cardiovascular, respiratory, neurologic, renal, or hepatic diseases by routine preoperative history, physical examination, and laboratory evaluation. Patients who were concurrently taking medications that would affect the central nervous system and/or the cardiovascular system were excluded. Their age range was 30–79 yr (mean ± SD 45.5 ± 11 yr). The weight range was 64–118 kg (mean ± SD 87 ± 14.8 kg). None of the patients received preoperative medication.

After an overnight fast, the subjects were brought to the operating room. An iv catheter was placed for drug and fluid administration. An arterial catheter was placed in the radial artery for continuous hemodynamic monitoring and blood sampling. A four-channel bipolar EEG was continuously recorded from leads C3-P3, C4-P4, Cz-P3, and Cz-P4 during the study, according to the International 10/20 system of electrode placement. EEG recording parameters and equipment were identical to our previous description.[5] The CCIP consisted of a Toshiba® T-3100 laptop computer and a Harvard® 22 Infusion Pump (Harvard Apparatus®, South Natick, MA). The thiopental pharmacokinetic data used in the CCIP has previously been described and its predictive performance quantitated.[5] The STANPUMP computer program was used in the CCIP.[6]

Figure 1 displays the sequence of the study events. A 5-min baseline recording of the EEG was obtained with the patient's eyes closed and with the patient breathing 100% oxygen through the anesthetic circuit and face mask. The CCIP then rapidly achieved and maintained the first target thiopental concentration randomly assigned between 10 and 30 μg/ml. After maintaining this target concentration for 5 min to allow serum:brain equilibration of thiopental, the patient was tested for verbal responsiveness. If the patient was still verbally responsive for an additional 2 min, the thiopental target concentration was increased to the second target level. If

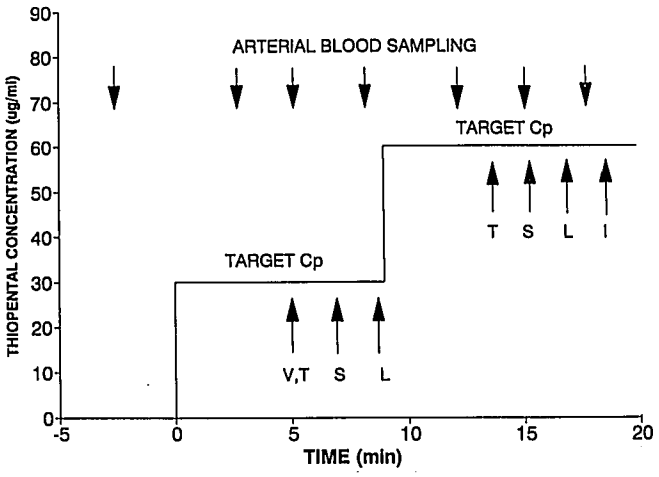

FIG. 1. The study design. Two target serum thiopental concentrations were achieved. Arterial blood sampling was obtained to measure blood gases and serum thiopental concentrations. Stimuli were applied as indicated. V = verbal stimuli; T = tetanic nerve stimulation; S = trapezius muscle squeeze; L = laryngoscopy; I = laryngoscopy and intubation.

the patient was unresponsive to verbal command, several noxious stimuli of 10-s duration were applied at 1-min intervals. These consisted of a 50-Hz constant electrical current that generated 50 mA to the forearm using a peripheral nerve stimulator to create neuromuscular tetanus (tetanic nerve stimulation), trapezius muscle squeeze, and direct laryngoscopy without intubation. Following these stimuli, a second, higher target serum thiopental concentration randomly assigned between 40 and 90 μg/ml was then rapidly achieved with the CCIP and maintained for 5 min. The same three noxious stimuli were repeated at 1-min intervals, followed by a laryngoscopy and intubation.

For the tetanic nerve stimulation and trapezius muscle squeeze, purposeful movement of an extremity was considered a positive response. For the laryngoscopy and laryngoscopy followed by intubation stimuli, in addition to purposeful movement of an extremity, any coughing or bucking during or immediately after the stimuli was considered a positive movement response. No other anesthetic drugs or muscle relaxants were used during the study. Ventilation was assisted as needed with a face mask and anesthesia circuit. Frequent arterial blood samples were collected prior to and during the study for measurement of serum thiopental concentrations and arterial blood gases (fig. 1).

The total (free plus bound) serum thiopental concentration were determined by a previously reported high-performance liquid chromatography assay.[7] For each target serum thiopental concentration, the mean of the two measured values (termed the constant serum thiopental concentration) obtained at least 5 min after achieving the

target was used in the subsequent pharmacodynamic analysis. The performance error of the CCIP was evaluated by calculating the median performance error (a measure of the systematic over or under achievement [bias] of the target level) and median absolute performance error, as described previously.[5,6] The median absolute performance error is a measure of the inaccuracy of the CCIP such that half of the performance errors will be greater than and half less than the median absolute performance error. A total of 111 measured serum thiopental concentrations were used in this data analysis.

The number of waves per second was derived from the EEG using the aperiodic waveform analysis methodology previously described.[5] The number of waves per second was smoothed using a moving average over a 10-s window. Using the constant serum thiopental concentrations and the quantal move/no move responses, the probability of no movement to each stimulus was modeled with the following expression:

$$\text{Probability of no movement} = \frac{Cp^{\gamma}}{Cp^{\gamma} + Cp_{50}^{\gamma}}$$

where Cp = measured constant serum thiopental concentration; Cp_{50} = constant serum thiopental concentration that will produce 50% probability of no movement to the noxious stimulus, and γ is the power function that describes the steepness of slope of the concentration *versus* effect relationship.

The Cp_{50} (± SE) for the movement responses to the stimuli were estimated with logistic regression.¶ The 95% confidence bounds were also estimated to determine if the responses to the stimuli were statistically different.

Results

No major complications occurred during the studies. Noxious stimuli were not applied to five patients at the first target serum concentration because they were arousable and responded to verbal commands. Due to difficulty visualizing the larynx secondary to the absence of muscle relaxants, the tracheas of six subjects could not be intubated. The arterial blood gases of all of the patients during the study were within normal limits, with mean (± SD) *p*H 7.39 (± 0.03), P_{CO_2} 42 (± 5.3), P_{O_2} 398 (± 140), and HCO_3 25.2 (± 2.2). When interviewed 24 h postoperatively, none of the subjects could recall the events that occurred during the study .

The measured, constant serum thiopental concentration *versus* time profiles for all of the patients at the two different target levels are shown in figure 2. Although

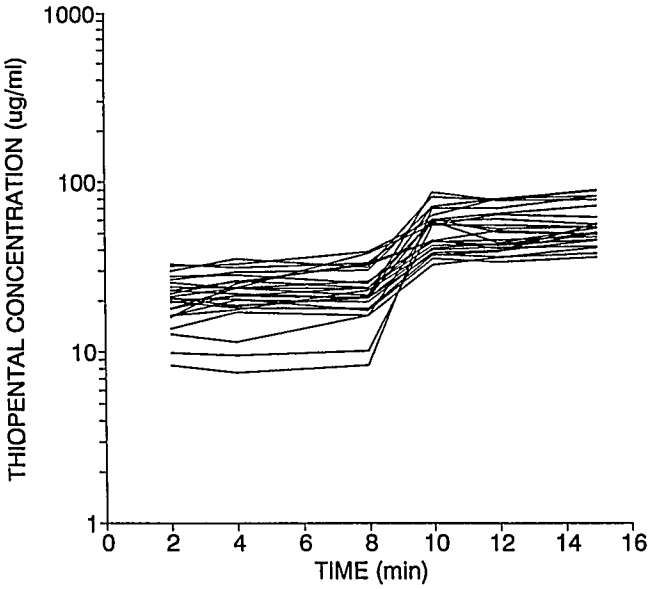

FIG. 2. The measured serum thiopental concentrations *versus* time for the two target thiopental concentrations in the 26 subjects.

there were slight variations of measured values at each target concentration during the study, the overall ability of the CCIP to achieve and maintain constant thiopental serum concentrations was satisfactory. The median absolute performance error, a measure of variability of the CCIP, was 18.5%, and the median performance error, a measure of bias, was +14%.

The relationship between the movement response and constant serum thiopental concentrations is shown in figure 3. For the five different stimuli, a pattern of consistent movement response at low constant serum thiopental concentrations was followed by an intermediate region at higher serum concentrations where both movement and no movement occurred followed by consistent lack of movement response at the highest serum concentrations. A rank order of progressively more intense stimuli can be seen in figure 3 from verbal to intubation stimulus. With the intubation stimulus, only three patients did not move despite constant serum thiopental concentrations approaching 90 μg/ml. Figure 4 displays the logistic regression analysis of the raw data. There is a family of curves that represent the probability of no movement relative to constant serum thiopental concentration. Table 1 presents the Cp_{50}, or constant serum thiopental concentration that produces a 50% probability of no response. Figure 4 displays the Cp_{50} values and the 95% confidence bounds of the estimate. The 95% confidence bounds of tetanic nerve stimulation and trapezius muscle squeeze overlap, indicating that the likelihood of movement in response to these two stimuli were not statistically different. The likelihood of movement in response to trapezius muscle squeeze were not statistically different from la-

¶ Wilkinson L: SYSTAT: The system for statistics. Evanston, IL, SYSTAT, Inc., 1988.

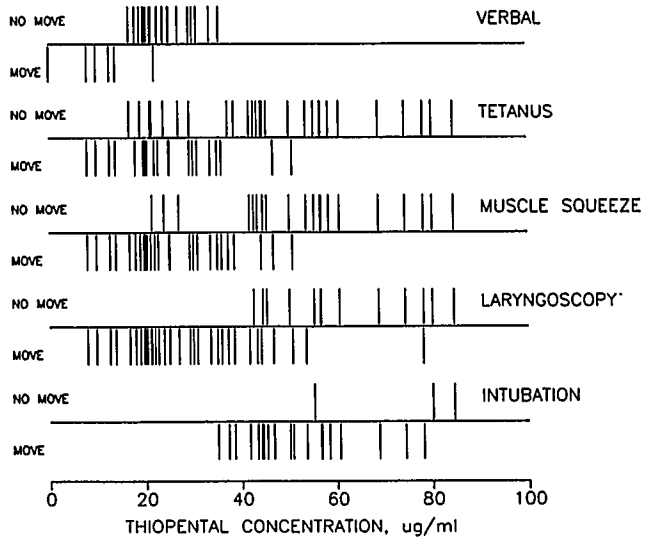

FIG. 3. The move/no move *versus* serum thiopental concentration for the five different clinical stimuli. Each bar indicates the serum thiopental concentration and response for stimuli applied to an individual patient.

ryngoscopy. The remaining stimuli were statistically different.

After visual inspection of all of the EEG recordings, the Cz-P3 lead appeared to be least affected by muscular movement and electromyographic interference during the study. This lead was used for subsequent analysis in all subjects. The biphasic relationship of the number of waves per second *versus* constant serum thiopental concentrations is shown in figure 5. At low concentrations of thiopental (15–20 μg/ml) there was an initial activation of the EEG, with an increase in the number of waves per second from the baseline. This was followed by a progressive decrease in the number of waves per second (*i.e.*, EEG slowing) with progressively higher serum thiopental concentrations. The EEG became isoelectric at serum thiopental concentrations greater than 50 μg/ml. Figure 6 displays the number of waves per second immediately before and after application of the noxious stimuli. There was no evidence of EEG activation when the stimuli were applied, even though the patients responded with clinical signs of inadequate anesthesia (movement).

The relationship of the number of waves per second to the presence or absence of the movement response from different stimuli is shown on figure 7. For the verbal, tetanic nerve stimulation and trapezius muscle squeeze, the biphasic relationship of constant serum thiopental concentration to the EEG number of waves per second confounded the data interpretation. Any EEG value greater than 8.5 waves/s (the awake baseline) can be associated with two different serum thiopental concentrations, a lower serum concentration during the EEG activation and then a higher serum concentration as the ac-

TABLE 1. Cp_{50} Values for Different Stimuli

Stimulus	Cp_{50} ± SE (μg/ml)	95% Confidence Limits (μg/ml)
Verbal	15.6 ± 1.1	13.4–18
Tetanus	30.3 ± 3.8	22.5–38
Trapezius squeeze	39.8 ± 3.3	33.1–46.4
Laryngoscopy	50.7 ± 2.9	44.8–56.5
Intubation	78.8 ± 7.4	63.4–92.4

Cp_{50} = constant serum thiopental concentration that produces a 50% probability of no movement response.

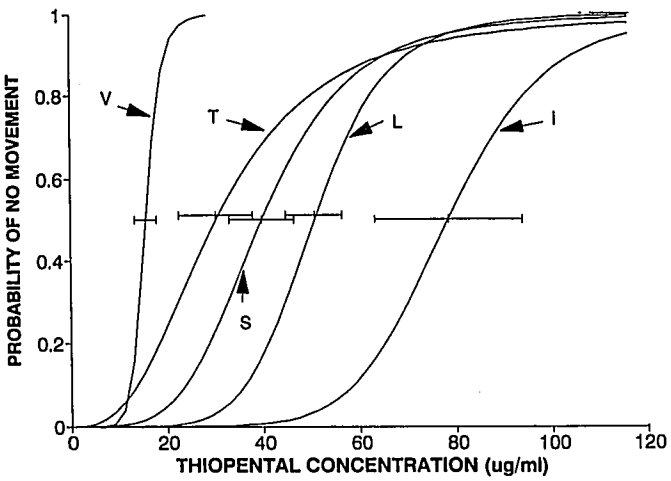

FIG. 4. The predicted probability of no movement *versus* serum thiopental concentrations, obtained using logistic regression of the data indicated in figure 3. The bars indicate the 95% confidence bounds of the estimate of the serum thiopental concentration producing a 50% probability of no movement response. V = verbal; T = tetanic nerve stimulation; S = trapezius muscle squeeze; L = laryngoscopy; I = laryngoscopy and intubation.

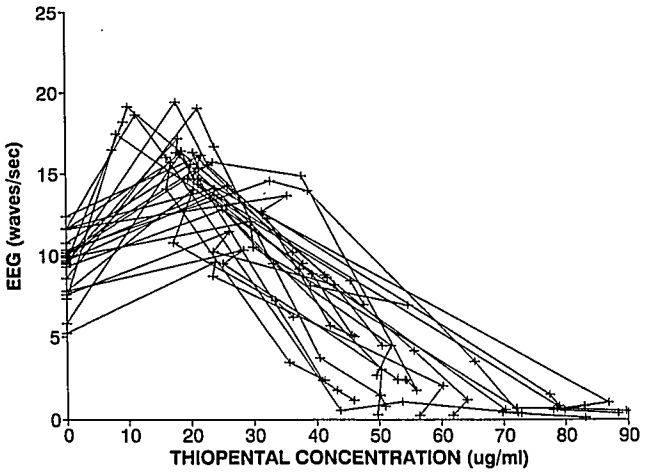

FIG. 5. The EEG waves per second *versus* measured constant serum thiopental concentration in the 26 subjects.

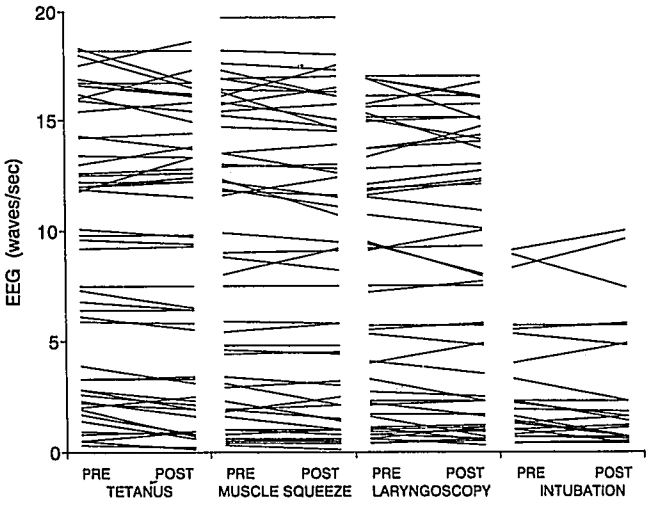

FIG. 6. The EEG waves per second pre- and postnoxious stimuli. No consistent trend of EEG activation or increasing waves per second could be seen with the different stimuli.

tivated EEG begins to slow. Thus, for the three less noxious stimuli (verbal, tetanic nerve stimulation, trapezius muscle squeeze) associated with lower serum thiopental concentrations, it was not possible to define a unique relationship between the number of waves per second and the presence or absence of movement. For laryngoscopy and laryngoscopy followed by intubation, movement responses occurred at low values of the EEG number of waves (0–3 waves/s) that are associated with a near isoelectric EEG.

Discussion

The assessment of clinical depth of anesthesia involves observing the responsiveness of a patient to a defined stimuli at a known and constant anesthetic drug concentration.[4] This approach has been best understood and applied to the inhalational anesthetics using the MAC methodology developed by Eger and associates over the past 25 yr.[3] The end-tidal, alveolar concentration was used as the site for measurement of drug concentration because it is the most readily measured index of equilibrium brain anesthetic tension. The initial skin incision and observation of movement response has been used successfully in humans as a reproducible, maximal, noxious stimulus and consistent response. Other stimuli and responses, more or less intense than skin incision and movement, have been described. These include verbal stimulus for eye opening (MAC-awake),[8] intubation and movement/coughing (MAC-intubation),[9] and skin incision with suppression of catecholamine release (MAC for blocking adrenergic response to incision [MAC-BAR]).[10]

Borrowing approaches used for the assessment of potent inhalational anesthetic depth, we have developed a method that can be applied to iv anesthetics like thiopental. The traditional bolus administration of iv anesthetic drugs prevents meaningful pharmacologic quantitation.[5] The CCIP allows constant iv anesthetic serum drug concentrations to be attained rapidly and then maintained and has obviated the limitation of rapid iv bolus administration. In the current study, the CCIP had a degree of accuracy and variability in surgical patients that was similar to what we observed in healthy volunteers.[5] The presence of noxious clinical stimuli and a wider age and weight range in the current study did not diminish the ability of the CCIP to obtain constant serum thiopental concentrations. The clinical movement responses seen following the multiple noxious stimuli did not appear to alter the pharmacokinetics of thiopental.

During the laryngoscopy and laryngoscopy followed by intubation stimuli coughing or bucking was used as a positive clinical response. When patients had coughing or bucking following laryngoscopy followed by intubation, movement of the extremities also occurred. It was difficult to separate purposeful from nonpurposeful movement of the extremities during this time, so we included coughing as a positive clinical response. MAC-intubation also used coughing and purposeful movement as the clinical response.[8] The movement responses may be associated with the spinal (brain stem in the case of laryngoscopy and intubation) reflexes to peripheral noxious stimuli. However, they also may be associated with light anesthesia and inadequate cortical CNS suppression, since most of these movement responses were associated with an increase of mean arterial pressure and heart rate. It is not possible for us to separate the cortical from spinal components of a movement or cough response.

The noxious stimuli we used differ from the skin incision used during the MAC measurement for potent inhalational anesthetics. We chose five different stimuli that were clinically relevant and justifiable during the induction of anesthesia using only thiopental. Figures 3 and 4

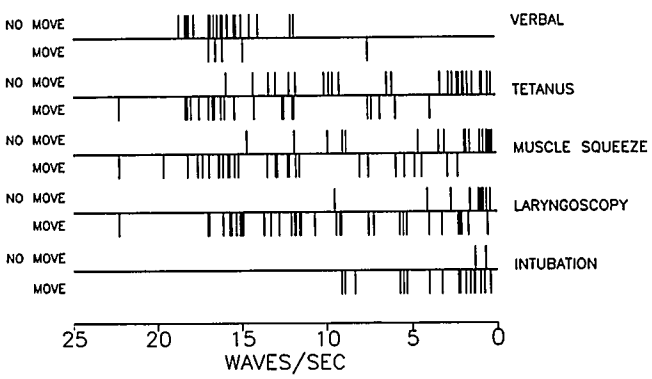

FIG. 7. The move/no move response *versus* EEG waves per second for the five different stimuli.

and table 1 demonstrate the progressive rank order of increasing constant serum thiopental concentrations necessary to create the transition from consistent movement response to no movement for the five different stimuli. The rank order of increasing drug concentration required to prevent movement response is compatible with the stimuli becoming progressively more intense. The least noxious stimulus was verbal responsiveness, with a Cp_{50} of 15.6 μg/ml, whereas the most noxious stimulus was laryngoscopy followed by intubation, with a Cp_{50} of 78.8 μg/ml. Only two pairs of stimuli were not statistically distinct; these were tetanic nerve stimulation *versus* trapezius muscle squeeze and trapezius muscle squeeze *versus* laryngoscopy. Becker has previously reported that serum thiopental concentrations that ablate the corneal reflex and responses to trapezius muscle squeeze and skin incision are essentially the same at 39–42 μg/ml.[11] We obtained a Cp_{50} value of 38.9 μg/ml for trapezius muscle squeeze, almost identical to what Becker reported.

Our data demonstrate that laryngoscopy followed by intubation is much more noxious than a laryngoscopy by itself. Yakaitis *et al.*[9] also found that significantly higher inhalational anesthetic concentrations are needed to ablate movement response to laryngoscopy followed by intubation relative to skin incision. Ausems *et al.* reported similar findings with the opiate alfentanil given with 70% nitrous oxide.[12] The significant innervation of the larynx and trachea may explain why, for three different anesthetic drugs, the intubation stimulus requires the highest anesthetic concentrations to ablate clinical response. Laryngoscopy followed by intubation can be considered the most noxious stimulus that has been quantitated with available methodology in humans. The constant serum thiopental concentrations necessary to ablate movement response to intubation are so high (greater than 80 μg/ml) that conventional induction doses of thiopental (4–5 mg/kg) do not achieve the biophase or site of action concentrations our study predicts are necessary to prevent movement. Clinical studies performed in the 1950s and repeated in the 1970s have demonstrated that hemodynamic responses to laryngoscopy and tracheal intubation are profound with conventional induction doses of thiopental (5–6 mg/kg).[13,14] Thiopental is known to be an effective hypnotic with few analgesic properties.[15] The high concentrations necessary to ablate the most noxious clinical stimulus demonstrated in our study may be a reflection of the lack of analgesia associated with thiopental hypnosis. Clinical practice has resulted in the addition of other anesthetic drugs with more analgesic efficacy (*i.e.*, opiates or inhalational anesthetics) to prevent unacceptable clinical sequela of inadequate anesthesia when thiopental is used as an induction agent.

There are some limitations of the methodology we used that could introduce error in our results. The logistic regression data analysis assumes that each measurement in a subject is independent and not correlated with any other measurements in that individual. Our study design had the following limitations relative to this assumption. 1) While two target serum thiopental concentrations were achieved in each individual, the lower concentration was always achieved before the higher value. 2) Except for intubation, each stimulus was applied twice to the same subject, resulting in possible intrasubject correlation and tolerance or sensitization. 3) Stimuli were not applied in a random manner, but rather in a sequence of least noxious stimulus progressing to the most noxious stimulus. 4) Except for verbal stimulation and tetanic nerve stimulation, the stimuli could not be standardized in an absolute manner. Even though most of the stimuli were applied by two of the investigators (SLS and DRS), it is likely that the magnitude of stimulation varied to some degree for trapezius muscle squeeze, laryngoscopy, and intubation. 5) For the intubation stimuli, only three nonresponses were recorded. Although this small amount of data was adequate for the logistic regression characterization, it would have been ideal to have higher thiopental serum concentrations and more nonresponses. We cannot assess the importance of the variation of stimuli on the pharmacodynamic data we have gathered. The tetanic nerve stimulation was performed for a precise period of time at a constant current (50 mA) and should represent a most reproducible stimulus.

Because of the concurrent perioperative use of anesthetic drugs with specific actions, such as muscle relaxants, β-blockers, and vasodilators, the traditional clinical signs of anesthetic depth such as movement and hemodynamic responses to noxious stimuli become less interpretable. This makes the monitoring of anesthetic depth more challenging to the anesthesiologist. The EEG has been suggested as a possible measure of anesthetic depth for halothane,[16] etomidate,[17] methohexitone,[18] isoflurane,[19] and propofol.[20] All of these studies have shown a relationship between the anesthetic drug concentration and various processed EEG measures that reflect the EEG response. Some of these studies have examined the clinical response to specific stimuli that may or may not be clinically relevant. However, none of the previous studies has directly attempted to correlate the EEG with clinical responses to relevant perioperative stimuli.

In the current study, we could not demonstrate a change of the EEG number of waves per second following the application of a series of noxious stimuli. In a canine investigation,[21] direct electrical stimulation of the sciatic nerve resulted in EEG activation when serum thiopental concentrations were between 15 and 27 μg/ml. In this canine study, no consistent activation of the EEG was seen during the application of sciatic nerve stimulation when serum thiopental concentrations were greater than 37 μg/

ml. We examined the EEG immediately before each noxious stimulus and for the next 15–30 s. We did not see any evidence of EEG activation (increase in number of waves per second) with any of the stimuli at a wide range of serum thiopental concentrations, despite patients' purposeful movements. It is possible that EEG activation would have been seen if the noxious stimuli had applied for a longer period of time. It is also possible that spinal and brain stem reflexes (as evident by the coughing/bucking to laryngoscopy/intubation) are present but may not be detected by the cortical EEG.

This study confirmed the biphasic EEG number of waves per second *versus* serum thiopental concentration relationship that we previously described.[5] Because in the current study only two constant serum thiopental concentrations were achieved in each patient, it was not possible to resolve the relationship of biphasic serum thiopental concentration *versus* number of waves per second in an individual subject, as we did previously.[5] The goal of the current study was to relate the EEG response to the clinical measures of anesthetic depth for the different noxious stimuli.

Loss of verbal responsiveness occurred during EEG activation at 12–18 waves/s relative to the awake baseline value of 8–12 waves/s. Movement response to tetanic nerve stimulation and trapezius muscle squeeze will occur if the EEG is activated and there are greater than 15 waves/s. Consistent lack of movement to tetanic nerve stimulation and trapezius muscle squeeze occurred only when there were fewer than 5 waves/s. The broad range of EEG waves/s from movement to no-movement (5 to 15) results from the biphasic concentration *versus* EEG response relationship where the same number of waves per second can occur at two different serum thiopental concentrations.

The biphasic relationship of serum thiopental concentration *versus* EEG number of waves per second complicates and limits the interpretation of the EEG as a measure of clinical depth. For serum thiopental concentrations greater than 30 μg/ml there is a progressive decrease in the number of waves per second as the serum thiopental concentration increases. Zero waves per second (isoelectric EEG with intermittent bursts) occurs at serum thiopental concentrations greater than 50 μg/ml. Figure 7 indicates that movement responses were common despite profound EEG slowing (0–3 waves/s). The EEG reached its maximal response (isoelectric signal) before consistent lack of movement occurred to the most noxious stimulus, laryngoscopy and intubation. Our data demonstrate the need to find an EEG parameterization that results in a monophasic response to increasing thiopental serum concentrations. The EEG parameter we used, number of waves per second from aperiodic waveform analysis, will not be practical as a monitor of depth of anesthesia for thiopental when it is used alone because of the biphasic effect and the inability to predict response to the most noxious stimuli. It is possible, however, by adding another anesthetic drug (*i.e.*, nitrous oxide or an opiate) that provides moderate analgesia, that the thiopental serum concentrations needed to achieve the lack of movement will decrease to a level where EEG response occurs.

In summary, we developed a method to assess clinical anesthetic depth for the iv anesthetic drugs. Our approach uses a CCIP to obtain constant serum concentrations over a clinically relevant range. Stimuli that vary in degree of noxiousness are then applied and the responsiveness of the patient observed. Using movement as the clinical measure of response and the measured constant serum thiopental concentrations, it is possible to quantitate the CNS sensitivity in a group of patients to the different stimuli. CNS sensitivity is estimated by the Cp_{50} for each stimulus. Our study demonstrates that extremely high serum thiopental concentrations are necessary to prevent movement response to laryngoscopy and intubation. We also examined the relationship of the EEG changes induced by thiopental to the clinical depth of anesthesia. The number of waves per second from aperiodic waveform analysis was used as a measure of thiopental EEG effect. The biphasic nature of the thiopental serum concentration–EEG relationship and the isoelectricity at high serum thiopental concentration complicate and limit the interpretation of the correlation between the EEG effect and the clinical responses. Using thiopental alone, movement to the profoundly noxious stimulation of laryngoscopy followed by intubation was observed in the presence of markedly slowed and isoelectric EEG waveforms.

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