

# *The Effect of High Dose Sodium Thiopental on Brain Stem Auditory and Median Nerve Somatosensory Evoked Responses in Humans*

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Median nerve somatosensory evoked potentials (MnSSEPs), brain stem auditory evoked responses (BAERs), and the cortical electroencephalogram (EEG) were recorded in six patients during a 62-min infusion of sodium thiopental (STP) at a rate of  $1.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (total dose,  $77.5 \text{ mg/kg}$ ). The EEG became isoelectric after  $22 \pm 8$  (SD) min of STP infusion. Dose-related changes in the latencies and amplitudes of various evoked response wave forms were observed. However, in no instance was any component of either the MnSSEP or the BAER rendered unobtainable by STP administration. For the MnSSEP, progressive increases in the central conduction time ( $5.33 \pm 0.41 \text{ ms}$  preinduction *vs.*  $7.46 \pm 1.2 \text{ ms}$  at  $t = 60 \text{ min}$ ) and in the latency of the cortical primary specific complex were observed simultaneously with significant reductions in the amplitude of the latter ( $2.10 \pm 0.85 \mu\text{V}$  preinduction *vs.*  $0.85 \pm 0.55 \mu\text{V}$  at  $t = 60 \text{ min}$ ). Changes in the latency and amplitude of the response recorded over the upper cervical spine (C2) were not statistically significant in this small population. For the BAER, progressive and significant increases in the latencies of Waves I, III, V (*e.g.*, Wave V latency:  $6.16 \pm 0.24 \text{ vs. } 6.87 \pm 0.31 \text{ ms}$ ) and in the I-III, III-V, and the I-V interwave latencies were observed. The amplitudes of the BAER components were not significantly altered. The authors conclude that the administration of a dose of STP in excess of twice that required to produce EEG isoelectricity can be compatible with effective monitoring of MnSSEPs and BAERs. However, STP produces dose-related changes in both evoked response wave forms, which must be considered in the interpretation of responses elicited during STP anesthesia. (Key words: Anesthetics, intravenous: thiopental. Brain: evoked potential. Monitoring: evoked potentials.)

THERE ARE CIRCUMSTANCES in neurosurgical anesthesia and intensive care in which the administration of EEG-suppressive doses of a barbiturate may be appropriate for either protective (focal cerebral ischemia) or therapeutic (elevated intracranial pressure) purposes. Electrophysiologic monitoring may be desirable in these same circumstances and, while the isoelectric cortical EEG can provide no information, sensory evoked responses

to both auditory<sup>1</sup> and peripheral nerve<sup>2</sup> stimulation have been shown to persist during barbiturate administration and therefore may still provide a useful means for obtaining information regarding the integrity of their respective neural pathways. However, accurate interpretation, particularly with respect to the avoidance of false positives requires a knowledge of the dose-related effects of barbiturates on evoked response wave forms. Our use of a high-dose sodium thiopental anesthetic regimen in the management of patients undergoing staged resection of giant intracranial arteriovenous malformations provided an opportunity to examine the effects of a very large dose of this agent ( $77.5 \text{ mg/kg}$ ) on brain stem auditory and median nerve somatosensory evoked responses (BAERs and MnSSEPs, respectively). The data obtained provide information as to the range of thiopental dosages compatible with effective evoked response recording and provide information that should facilitate accurate interpretation of evoked responses obtained during the administration of this agent.

## Methods

The protocol was approved by the Committee on Investigations Involving Human Subjects of the University of California, San Diego. Informed consent was obtained from six patients (mean age  $28.8 \text{ yr}$ ; range  $22\text{--}43 \text{ yr}$ ) undergoing staged resection of giant arteriovenous malformations (AVMs). All patients were intellectually intact, and any neurologic deficits (see table 1) were unilateral. All patients were receiving either prophylactic or therapeutic anticonvulsants (see table 1) at the time of study.

Premedication consisted of lorazepam,  $2\text{--}4 \text{ mg}$  po the evening before surgery, and diazepam,  $5\text{--}10 \text{ mg}$  po 30 min before transfer to the operating room. In the operating suite, additional diazepam,  $5\text{--}10 \text{ mg}$  iv, and, occasionally, morphine,  $2\text{--}5 \text{ mg}$  iv were administered to provide sedation during the placement of monitoring devices, which included a pulmonary artery catheter and a radial arterial line. The intravenous catheter was placed contralateral to the AVM in order to avoid inadvertent temperature change in the extremity that was to be stimulated for MnSSEP determinations.

MnSSEPs were recorded in all six patients, and BAERs were recorded in 4. A Nicolet Pathfinder II® was

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TABLE 1. Patient Data

Patient	Age/Sex	AVM	Presentation	Neurologic Examination	Medications*
1	21/M	R. Temporal	Seizures	Normal	Dilantin
2	42/F	L. Basal ganglia	Headache	Mild R. hemiparesis	Dilantin
3	27/F	R. Thalamic	IVH†	L. Hemiparesis	Dilantin
4	31/F	R. Temporal-parietal	Seizures	Expressive dysphasia	Dilantin Phenobarb Theophylline
5	21/F	R. Basal Ganglia	IVH	L. Hemiparesis	Phenobarb
6	24/M	R. Trigone	IVH	Normal	Dilantin Hydralazine Aldomet

\* All patients received preoperative lorazepam, diazepam (see "Methods"), and dexamethasone.

† IVH = intraventricular hemorrhage.

employed for evoked response recording, and detailed stimulus and recording parameters are given in table 2. For both modalities, recording electrodes were gold disks (Grass) and impedances were maintained at less than 3 k $\Omega$ . For the BAERs, alternating condensation and rarefaction click stimuli were generated with Stanton® model BR22B7. 5NP transducers and delivered via a polyethylene ear insert, available from Nicolet Biomedical. For the MnSSEPs, stimulation of the median nerve was accomplished via subdermal platinum needles (Grass). The anode was placed at the level of the radial styloid, and the cathode was 3 cm proximal thereto. The responses recorded for study purposes were elicited by stimulation of the median nerve ipsilateral to the AVM. Recordings were made from electrodes located over the brachial plexus (Erb's point), over the upper cervical spine (at the level of the spinous process of the second cervical vertebra—C2), and over the contralateral

sensory cortex. For the latter wave form, the initial negative deflection of the primary specific complex, the nominal N<sub>20</sub> (poststimulus latency approximately 19–20 ms) and the subsequent positive deflection are referred to herein as N1 and P1, respectively. The central conduction time (CCT), the interval between the negative wave at C2, the nominal N<sub>14</sub> (poststimulus latency approximately 14 ms), and N1 was noted. Figure 1 presents an example of the three MnSSEP wave forms recorded.

For approximately 5 min before and throughout the barbiturate infusion, a two-channel electroencephalogram (FP1-O1, FP2-O2, International 10–20 System) was also recorded from subdermal platinum needles in five of the six patients. The EEG was recorded on paper (Beckman Accutrace®) and on magnetic tape.

TABLE 2. Evoked Response Stimulation and Recording Parameters

	BAER	MnSSEP
Stimulus	Alternating clicks	DC square wave
Intensity	Sensory threshold + 70 dB	Motor threshold + 20%
Masking	40 dB white noise contralateral	
Duration	100 $\mu$ s	100 $\mu$ s
Frequency	11.1 Hz	3.1 Hz
Repetitions	2,000	200
Montage*	Cz-A1 Cz-A2	C3' or C4'—FPz C2—FPz Erb's Point—FPz
Ground	FPz	A1
Filters	150–3,000 Hz	30–250 Hz
Time base	10 ms	40 ms
Amplification	3.0 $\times 10^5$	1.2 $\times 10^5$

\* International 10–20 system. C3' and C4' are 1 cm posterior to C3 and C4.

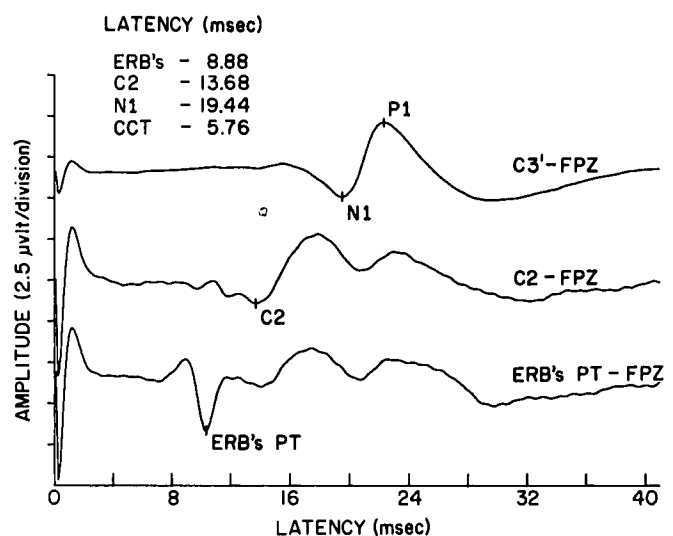


FIG. 1. Evoked responses to median nerve stimulation recorded over the brachial plexus (Erb's point), the upper cervical spine (C2), and the sensory cortex (C3' or C4'). Positive deflections are upward.

TABLE 3. Median Nerve SSEP Latencies and Amplitudes versus Serum Thiopental Concentration

Time (min)	Thiopental (μg/ml)	Latency (ms)					Amplitude (μV)		
		Erb's	C2	N1	P1	CCT	N1-P1	Erb's*	C2*
0	—	10.2 ± 1.1	13.6 ± 1.8	19.0 ± 1.8	22.6 ± 1.8	5.3 ± 0.4	2.1 ± 0.8	2.7 ± 0.9	2.7 ± 1.4
5	—	10.3 ± 1.2	13.7 ± 1.8	19.9 ± 2.5†	23.3 ± 2.5†	6.2 ± 1.0†	2.1 ± 1.3	2.7 ± 0.5	2.3 ± 1.1
15	35 ± 13	10.2 ± 1.0	13.7 ± 1.6	20.5 ± 2.6	23.8 ± 2.8	6.8 ± 1.2	1.4 ± 0.5†	2.7 ± 0.7	2.1 ± 0.9†
30	51 ± 17	10.4 ± 1.0	14.0 ± 1.7	21.0 ± 2.3	24.9 ± 2.5	6.9 ± 1.2	1.2 ± 0.9	2.6 ± 0.9	2.0 ± 0.9
45	66 ± 25	10.4 ± 0.9	14.0 ± 1.7	21.3 ± 2.2	25.8 ± 2.7	7.2 ± 1.1	1.0 ± 0.7	2.2 ± 1.2	2.1 ± 0.7
60‡	75 ± 36	10.5 ± 0.9	14.3 ± 1.8	21.8 ± 2.3	25.9 ± 2.5	7.5 ± 1.2	0.9 ± 0.6	2.2 ± 1.1	1.8 ± 0.6
P§	—	NS	NS	P < 0.01	P < 0.01	P < 0.01	P < 0.01	NS	P < 0.05

\* Amplitude from the negative deflection (see fig. 1) to the ensuing positive deflection.

† Earliest interval significantly different ( $P < 0.05$ ) versus  $t = 0$  min.

‡ For  $t = 60$  min,  $n = 5$ . For all other intervals,  $n = 6$ .

§ Repeated measures analysis of variance of data for  $t = 0, 5, 15, 30$ , and  $45$  min.

After placement of monitoring devices, noise and activity in the room were curtailed, hearing thresholds were determined, and baseline BAERs and MnSSEPs were recorded in duplicate. Each pair of responses was compared for reproducibility and a baseline "grand-average" was generated by adding the two. A 10-min rest period ensued and, at its conclusion, an infusion of sodium thiopental was begun at a rate of  $1.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . When loss of consciousness appeared imminent (approximately  $t = 3$  min), pancuronium and metocurine were administered and ventilation was controlled by mask ( $\text{FI}_{\text{O}_2}$ , 0.5; end-tidal  $\text{CO}_2$  by mass spectrometry, 4.0–4.5%). Repeat MnSSEP determinations were performed at  $t = 5, 10, 15, 20, 25, 30, 45$ , and  $60$  min. BAER determinations were repeated at  $t = 17, 32, 47$ , and  $62$  min. A nasotracheal tube was inserted immediately following data collection at  $t = 47$  min, but no other stimuli were permitted during the period of study. In accordance with the protocol of a simultaneous study of the hemodynamic effects of thiopental, lactated Ringer's solution was administered in sufficient quantity to maintain pulmonary artery occlusion pressure at the preinduction level. Pulmonary artery temperature (Edwards Swan-Ganz® catheter) was maintained at preinduction levels with the use of fluid warmers, a heater/humidifier, and warming blankets.

Specimens of arterial blood were drawn at  $t = 15, 30, 45$  and  $60$  min for serum thiopental assay by high-performance liquid chromatography.<sup>3</sup>

#### DATA ANALYSIS

To determine whether thiopental produced significant changes in the latency and amplitude of the various evoked response wave forms, the values obtained were examined by a repeated measures analysis of variance. Where a significant change in a given parameter was identified, pairwise comparisons were performed between the preinduction value and the values obtained at successive intervals in order to determine at what pentothal

dosage the change became significant. These pairwise comparisons employed the Bonferroni  $t$  test with appropriate corrections for multiple comparisons as described by Glantz.<sup>4</sup>

#### Results

Pulmonary artery temperature remained within  $0.5^\circ \text{C}$  of preinduction levels in all patients. Cardiac output was similarly well maintained. The mean cardiac index ( $1 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) was  $4.0 \pm 0.6$  (SD) before induction and  $3.7 \pm 1.0$   $1 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  after  $60$  min of sodium thiopental infusion (total dose,  $75 \text{ mg/kg}$ ). The mean arterial pressure decreased from  $85 \pm 4$  mmHg preinduction to  $66 \pm 9$  mmHg at  $t = 60$  min. § Arterial blood gas and haemoglobin values for specimens drawn preinduction and at  $t = 60$  min ( $\text{FI}_{\text{O}_2}$  0.5 for both) were as follows: preinduction;  $\text{Pa}_{\text{O}_2}$ ,  $233 \pm 7$  mmHg,  $\text{Pa}_{\text{CO}_2}$ ,  $39 \pm 5$  mmHg;  $\text{pH}$ ,  $7.39 \pm 0.03$ ; and Hb,  $12.9 \pm 1.6$  g/dL; and at  $t = 60$  min:  $\text{Pa}_{\text{O}_2}/240 \pm 28$  mmHg;  $\text{Pa}_{\text{CO}_2}$ ,  $40 \pm 8$  mmHg;  $\text{pH}$ ,  $7.40 \pm 0.11$ ; and Hb,  $12.1 \pm 1.6$  g/dL. The decrease in haemoglobin was occasioned by the administration of lactated Ringer's solution in sufficient quantity to maintain pulmonary artery occlusion pressure at preinduction levels. The lowest observed haemoglobin was  $10.1$  g/dL.

The electroencephalogram became isoelectric after  $22.2 \pm 7.5$  min of thiopental infusion. Errors in handling and shipment resulted in the loss of the thiopental levels for three of the six patients. Therefore, no statistical analysis of the concentration-related effects of thiopental was attempted. However, the thiopental data obtained in the remaining three patients in the present study together with data obtained in an additional five subjects undergoing hemodynamic study during an identical thiopental infusion are presented here and in table 3 for reference. For the eight patients, serum thio-

§ An abstracted description of the hemodynamic effects of this anesthetic regimen has been presented previously<sup>5</sup> and a detailed report is in press.

TABLE 4. BAER Latencies and Amplitudes *versus* Time

Wave → Time (min)	Latency (ms)			Amplitude (μV) Vp-Vn
	I	III	V	
0	1.94 ± 0.07	4.29 ± 0.16	6.16 ± 0.24	0.44 ± 0.29
17	2.03 ± 0.09*	4.44 ± 0.13*	6.53 ± 0.23*	0.33 ± 0.11
32	2.03 ± 0.06	4.56 ± 0.18	6.76 ± 0.26	0.29 ± 0.12
47	2.03 ± 0.05	4.62 ± 0.19	6.87 ± 0.31	0.29 ± 0.11
62†	2.09 ± 0.10	4.66 ± 0.32	6.83 ± 0.36	0.32 ± 0.11
P value‡	P < 0.05	P < 0.01	P < 0.01	NS

\* Earliest interval significantly different ( $P < 0.05$ ) *versus*  $t = 0$  min.

† For  $t = 62$ ,  $n = 3$ . For all other intervals,  $n = 4$ .

‡ Repeated measures analysis of variance of data for  $t = 0, 17, 32$ , and 47 min.

pental levels increased to a level of  $75 \pm 36 \mu\text{g/ml}$  at  $t = 60$  min.

Technically satisfactory evoked responses were obtained in all patients. However, a cable malfunction resulted in the failure to obtain the final MnSSEP ( $t = 60$  min) and BAER ( $t = 62$  min) recordings for one patient. Accordingly, the statistical analysis examines only the data obtained up to and including  $t = 45$  min for MnSSEPs and  $t = 47$  min for BAERs. The data obtained at  $t = 60$  and  $t = 62$  min ( $n = 5$  and 3, respectively) are presented for information in tables 3 and 4.

In no instance did the administration of sodium thiopental (77.5 mg/kg over 62 min) result in the obliteration of any BAER or MnSSEP wave form. The effect of increasing thiopental dose on both evoked response modalities was, in general, characterized by an

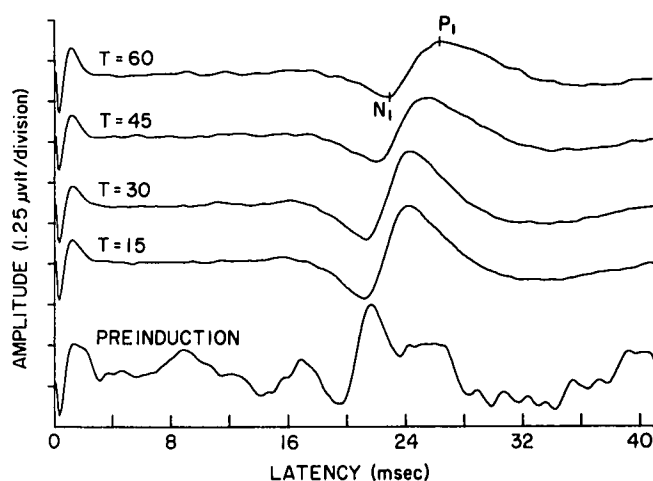


FIG. 2. The somatosensory evoked response (C3'-FPz) to right median nerve stimulation preinduction and at intervals during the infusion of sodium thiopental at a rate of  $1.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The initial negative and the succeeding positive deflections of the primary specific complex are designated N1 and P1, respectively. Positive deflections are upward.

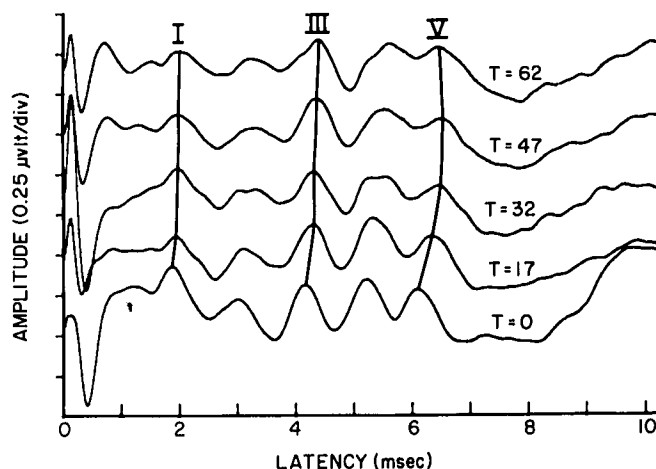


FIG. 3. The brain stem auditory evoked response (Cz-A1) preinduction and at intervals during the infusion of  $1.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  of sodium thiopental. The bars identify the peaks of Waves I, III, and V. Positive deflections are upward.

increase in the latency and a decrease in the amplitude of the various wave forms.

### MnSSEP

There were significant increases in latency for N1, P1, and for the central conduction time (all,  $P < 0.01$ ) (see Figs. 1 and 2, and table 3). There were significant decreases in the amplitudes of the C2 ( $P < 0.05$ ) and N1-P1 ( $P < 0.01$ ) wave forms.

### BAER

Thiopental administration resulted in only minor alteration in the BAER (see fig. 3, and table 4). Nonetheless, there were significant increases in the latencies of waves I ( $P < 0.05$ ), III, and V (both,  $P < 0.01$ ), and in the interwave latencies for the I-III, III-V, and I-V intervals (all,  $P < 0.05$ ). An apparent decrease in the amplitude of wave V (as measured to the subsequent negativity, Vn) was not statistically significant.

With respect to the latency increases observed for both modalities, later waves were, in general, more markedly affected. For instance, at  $t = 62$  min, the latency increases for BAER waves I and V were 7.7 and 13.1%, respectively; and for the MnSSEP, the increases in the upper cervical and N1 components of the MnSSEP response were 5.2 and 14.7%, respectively.

### Discussion

There has been only limited prior study of the effects of sodium thiopental on evoked responses in humans. However, the available data, in general, reflect the

resilience of the MnSSEPs and BAERs that we have observed. Ganes and Lundar<sup>2</sup> recorded MnSSEPs in six cerebrally injured patients receiving thiopental infusions to prevent anticipated elevations of ICP. Initial recordings were made at a thiopental level sufficient to produce either a slow wave (theta or delta) or burst suppression pattern and were repeated after administration of sufficient additional thiopental to produce isoelectricity. As was the case in our study, these authors observed that in all instances MnSSEPs were recordable during thiopental administration. However, they concluded that increasing barbiturate concentrations produced no alterations in MnSSEP wave forms or in central conduction time. These latter observations stand in sharp contrast to the results of our study, which demonstrated dose-related changes in both CCT and the morphology of the primary specific complex. The explanation of this discrepancy is not certain. However, it is possible, because the concentration range over which their study was performed was relatively narrow, that any changes that may have occurred were too small to be detectable. In addition, if a method other than subjective comparison of wave forms was used in comparing primary specific complex morphologic characteristics, it was not described.

Abrahamian *et al.*<sup>7</sup> recorded the cortical response to median nerve stimulation in surgical patients and observed that incremental administration of 6–8 mg/kg of thiopental occasionally produced increases in the latency of the primary specific complex. We consistently observed latency increases (the effect on amplitude was variable) at a dose of 7.5 mg/kg ( $t = 5$  min), and any difference between the Abrahamian study and the present results probably was occasioned by a more rapid rate of administration of thiopental in the present study. Ikuta<sup>8</sup> also administered thiopental, 4 mg/kg, to human subjects and observed increases in latency and variable changes in the amplitude of the early cortical response to median nerve stimulation.

Angel and Gratton<sup>9</sup> recorded cortical responses to forepaw stimulation in urethane-anesthetized rats. They administered thiopental in increments of 12.5 mg/kg (time course not specified) and observed dose-related increases in latency and decreases in amplitude similar to those seen in our human subjects. While they observed a persistent cortical response at a total dose of 75 mg/kg (our maximum dose), the response was ultimately lost at a total dose of 100 mg/kg. Accordingly, it is possible that in humans the progressive attenuation of the cortical response that we observed might similarly progress to obliteration at extremely high serum levels. However, our patients received thiopental doses in excess of twice those necessary to render the cortical EEG isoelectric. Therefore, patients receiving thiopental in

other circumstances rarely should achieve serum levels beyond the range examined herein.

There is only a single human report that examines the effects of thiopental on BAERs. Duncan *et al.*<sup>10</sup> observed no changes in BAERs when 4 mg/kg of thiopental was administered to lightly anesthetized (halothane) children. The lowest dose at which we evaluated the BAER was 19 mg/kg and, while we detected alteration (increased latency), the effect was minor, and our observations are probably consistent with those of Duncan *et al.*<sup>10</sup> The relative resistance of the BAER to barbiturate effects has been observed previously in humans following self-administered overdoses of short-acting barbiturates<sup>1</sup> and in cats following incremental administration of 180 mg/kg of pentobarbital.<sup>11</sup>

It was the subtentorial responses (the BAER and the C2 component of the MnSSEP) that were the more resistant to the effects of thiopental, and it was the cortical response (of the MnSSEP) that was most markedly affected. The greater percentage change in the latencies and amplitudes these later waves is consistent with the notion that, while barbiturates alter both axonal conduction and synaptic transmission, it is the latter that is more profoundly affected.<sup>12</sup> The neural pathways leading to the generators of later waves probably involve a greater number of synapses and therefore might be expected to be more vulnerable to the effects of thiopental. The persistence of the cortical evoked response is also consistent with an existing hypothesis regarding the mechanism of action of barbiturates (and certain other anesthetics). That hypothesis suggests that the neuronal suppression that is manifested by a decrease in EEG activity and cerebral metabolic rate is not accomplished exclusively by global depression of neurons and synapses but to some extent by a more specific action on neurons (probably in the reticular activating system) that control level of arousal or basal activity.<sup>13</sup> While EEG isoelectricity indicates depression of cortical function, the continued presence of the evoked response indicates that the capacity to function has not been entirely suppressed. Furthermore, the present data indicate that additional suppression (as manifested by increases in latency and decreases in amplitude) in fact occurs as drug levels increase beyond the point of isoelectricity. However, the locus and mechanism of that progressive suppression are unknown.

The possibility does exist that the progressive changes in evoked responses that we observed beyond the point of isoelectricity represent toxicity rather than suppression of function. However, this seems unlikely. Michenfelder<sup>14</sup> measured brain concentrations of ATP, phosphocreatine, lactate, and pyruvate after the administration of 177 mg/kg of thiopental to dogs and concluded that thiopental caused no adverse effects on cerebral metabolic

pathways. Furthermore, no patient in the present study group showed postoperative evidence of either focal or nonspecific neurologic deterioration.

It should be noted that the stimulus and recording parameters that were employed in the present study may have influenced the results that were obtained. Attenuation of wave forms is known to occur with increasing stimulus frequencies and accordingly we selected stimulus rates that were as slow as was consistent with our attempts to record discreet points in a dynamic process. It is possible that the thiopental-related changes that were observed would have been lessened by a slower stimulus rate. In addition, the amplifier band pass filters also can influence the composition, amplitude, and latency of the recorded wave forms. This will be of greatest relevance in comparisons of the absolute values obtained in investigations in which different filter parameters are employed. The parameters were constant throughout the present study, and it is likely that relative changes in latency and amplitude that are reported are indicative of those that would be observed at other filter settings.

The data presented herein are relevant to any patient undergoing evoked response monitoring during thiopental anesthesia. However, the greatest relevance may be to those patients in whom the EEG is deliberately suppressed and is therefore of no value as an electrophysiologic monitor. Our data indicate that, when suppression is accomplished with thiopental, evoked response monitoring can be a feasible monitoring alternative. It should be noted that our results were obtained during study of normal neural pathways. It is entirely possible that evoked responses that are initially abnormal and attenuated will be lost as a result of thiopental administration.

In summary, our results indicate that neither BAERs nor MnSSEPs are abolished by a dose of thiopental (77.5 mg/kg), which is in excess of twice that required to produce isoelectricity of the cortical EEG. Accordingly, we conclude that effective monitoring of these pathways can be accomplished during this form of anesthesia and that loss of the evoked response in these circumstances should not be ascribed to thiopental administration. However, the interpretation of changes in evoked responses observed during barbiturate administration must

take into account the dose-related changes in latency and amplitude that we have observed.

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