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Effects of Thiopental, Fentanyl, and Etomidate on Upper Extremity Somatosensory Evoked Potentials in Humans

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The effects of three anesthetic induction agents on somatosensory evoked potentials (SEP) were assessed in unpremedicated patients who were without neurologic abnormality of the upper extremities. SEP was assessed by stimulation of the nondominant median nerve and responses were recorded over Erbs point (N10), second cervical vertebra (N14), and the contralateral cortex (P15, N20, P23 latencies, and P15–N20 and N20–P23 amplitudes). Nine patients received thiopental (4 mg/kg, iv bolus), nine patients received fentanyl (25 μg/kg, iv bolus), and nine patients received etomidate (0.4 mg/kg, iv bolus). SEP was assessed before and after drug administration at motor threshold stimulus intensity. Thiopental increased the latency of N10, N14, and N20. The amplitudes of N10-, N14-, and scalp-recorded waves were not altered by thiopental. Fentanyl increased N20 and P23 latency and decreased the amplitude of P15–N20. Etomidate increased latency of N20 and P23 without alteration of latencies of N10 or N14 and increased the amplitude of P15–N20 and N20–P23, while the amplitude of N10 was unchanged and the amplitude of N14 was decreased. It is concluded that thiopental or fentanyl causes only modest alterations in early waves of upper extremity SEP, whereas etomidate increases the amplitude of scalp-recorded waves. The effect of etomidate on SEP may make diagnosis of neurologic injury more difficult because of the changing waveform. (Key words: Anesthetics, intravenous: fentanyl; etomidate; thiopental. Measurement techniques: somatosensory evoked potential. Monitoring: somatosensory evoked potential.)

SOMATOSENSORY EVOKED POTENTIALS (SEP) are useful in assessing neurologic injury during a variety of spinal and cranial operations.[1–3] Although initially used to detect neurologic injury caused by distraction during Harrington rod placement in neurologically normal patients,[1,2,4] the intraoperative use of SEP also includes patients with preexisting spinal[5] and intracranial pathology.[3] Intraoperative monitoring of patients with preexisting neurologic abnormalities requires information on the effects of anesthetic drugs because these drugs may directly alter the SEP, thus interfering with monitoring.

A lack of alteration of anesthesia level should facilitate diagnosis of neurologic insult and allow rapid demonstration of cause and effect during both the insult and recovery. The anesthetic technique in patients at risk of neurologic injury is chosen to maximize hemodynamic stability and minimize alterations in oxygen delivery to neural tissue at risk. The use of intravenous agents and relatively low concentrations of inhalational agents appears to meet the criteria of hemodynamic stability, maintenance of SEP waves suitable for monitoring (even in patients with abnormally small SEP), and rapid awakening for serial neurologic examinations.[6] In addition to supplementation of anesthetic gases, intravenous agents may be useful in patients with head injury to reduce or control intracranial pressure.[7,8]

In the present study we assess and compare the effects of commonly used intravenous agents (thiopental, fentanyl, and etomidate) on SEP in patients who have received no other anesthetic agents.

Methods

The effect of anesthetic induction with intravenous agents was studied in 27 unpremedicated patients. The study was approved by the Johns Hopkins institutional human studies committee and each patient gave informed consent prior to the study. Patients qualified for this study if they were free of symptoms or signs of upper extremity neurologic abnormality and had no contraindication to deletion of anesthetic premedication. The patients all underwent lumbar or lower thoracic spinal surgery. The patients were assigned to three study groups on a rotational basis. Group 1 patients (n = 9) received thiopental (Pentothal® 4 mg/kg, iv bolus), Group 2 patients (n = 9) received fentanyl (Sublimaze® 25 μg/kg, iv bolus) and Group 3 patients (n = 9) received etomidate (Amidate® 0.4 mg/kg, iv bolus). The drug doses were chosen because they are used clinically to induce anesthesia in neurosurgical patients. Immediately after loss of consciousness (failure to respond to verbal command; loss of lid reflex) each patient received pancuronium (0.1 mg/kg, iv bolus). Blood pressure was measured by auscultation and mean arterial blood pressure (MAP) was calculated as diastolic pressure plus 33% of pulse pressure. End-tidal CO_2 was measured using a Hewlett Packard Capnograph (model 47210A). The patients were manually ventilated to maintain an end-tidal CO_2 of 35–40 mmHg during the period of the study, and intubation was postponed until data collection was complete. Because of the potentially short action of thiopental and etomidate, the study was limited to only one upper extremity. Cup electrodes were placed over the contralateral cortex (C'_3 or C'_4) and over the sec-

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TABLE 1. Age, Height, and Blood Pressure Response to Drug Administration

	Age (yr)	Height (in)	MAP	
			Preinduction (mmHg)	Postinduction (mmHg)
Thiopental (n = 9) (4 mg/kg)	43 ± 5 (24–70)	68 ± 2 (66–71)	93 ± 5	95 ± 5
Fentanyl (n = 9) (25 μg/kg)	49 ± 6 (21–74)	67 ± 1 (62–72)	102 ± 3	102 ± 4
Etomidate (n = 9) (0.4 mg/kg)	46 ± 2 (28–72)	67 ± 2 (60–72)	95 ± 6	92 ± 5

Data presented as mean ± SEM (range). MAP = mean arterial pressure.

ond cervical vertebra (SC-2) and were referenced to a cup electrode at F_{PZ} (international 10–20 system). The electrodes were filled with conductive gel and impedance was decreased to <2 kohm by dermal abrasion. A disposable electrode (impedance <3 kohm) was placed over Erbs point (EP) and referenced to F_{PZ}. The median nerve of the nondominant hand was stimulated with a transcutaneous stimulator to determine a location that caused a distinct digital twitch. Sterile needle electrodes (23 gauge) were then placed and secured. SEP was recorded using a Nicolet® Med 80 (Nicolet Biomedical, Madison, WI). A stimulus intensity just sufficient to produce a digital twitch was used (1.9–3.9 mamp). In the awake patient, 512 stimuli were delivered at 5.9/s and averaged. Following induction of anesthesia, 128–256 stimuli were delivered at 5.9/s and averaged. Replicate waves were assessed in all patients for each study period. However, only the initial waveform in each patient for each period was used for analysis. Band pass filters of 15–1500 Hz were used. Large-voltage artifact was automatically rejected by the computer. All data were stored on magnetic disk for later analysis. The initial negative waves at EP and SC-2 and early scalp-recorded waves were assessed using the cursor mode of the computer.

The wave at EP was a negative deflection occurring about 10 ms following stimulation (N10). The latency was determined at the peak of the wave. The amplitude was measured from baseline to the wave peak. The initial negative wave at SC-2 occurred approximately 14 ms after stimulation (N14) and was evaluated in a similar manner. Scalp-recorded waves occurring 15–30 ms after stimulation were evaluated. Those waves are easily developed in the unpremedicated patient and are relatively unaffected by anesthetic gases. P15, an early positive wave, occurred approximately 15 ms after stimulation and because of its small size, amplitude was not assessed. The initial negative wave recorded on the scalp (N20) occurred approximately 20 ms after stimulation, and the amplitude (P15–N20) was measured from the trough of P15 to the maximum negative deflection of N20. A positive wave (P23) followed N20. The latency of P23 was measured at its maximum positive deflection, and amplitude of N20–P23 was measured from the maximum negative deflection of N20 to maximum positive deflection of P23. Data accumulation following loss of consciousness required 1–2 min, including generation of replicate waves.

The effect of the vehicle of etomidate (35% propylene glycol) was assessed in volunteers (n = 6). This part of the study was separately approved by the Human Studies Committee, and each subject gave written permission. SEP was determined as in Groups 1–3. SEP was determined before and 90 s following injection of a volume of 35% propylene glycol equal to that which the subject would have received had they received etomidate (0.4 mg/kg) for induction of anesthesia.

Data in text, tables, and figures are presented as mean ± SEM. Analysis of variance (ANOVA) for between-within design was used to compare effects of thiopental, fentanyl, and etomidate on amplitude and latency at the various electrode locations. ANOVA was also used to compare the effect of the drugs on MAP. If ANOVA demonstrated an effect ($P < 0.05$), Duncan's multiple range test was used to test for significant differences.

Results

Satisfactory data was obtained from all patients. Despite the lack of premedication, no patient voiced unpleasant memory of preinduction events, and there was no memory of intraoperative events, specifically intubation.

The Groups (1–3) were comparable in age and height (table 1). The increased age of the patient groups reflects the nature of the diseases requiring surgery. Approximately 50% of each group were female. Anesthesia induction did not significantly alter blood pressure in any of the three groups (table 1).

Figure 1 shows scalp-recorded waves before and after induction of anesthesia with thiopental (4 mg/kg), fentanyl (25 μg/kg), or etomidate (0.4 mg/kg). The effects of anesthetic agents (thiopental, fentanyl, etomidate) on wave latencies measured at EP, SC-2 and contralateral scalp for Groups 1–3 are shown in figure 2. Thiopental increased the latency of N10, N14 and N20 above control without alteration of latency P15 or P23. Fentanyl increased the latency of N20 and P23 without alteration of latency of N10, N14, or P15. Etomidate increased the

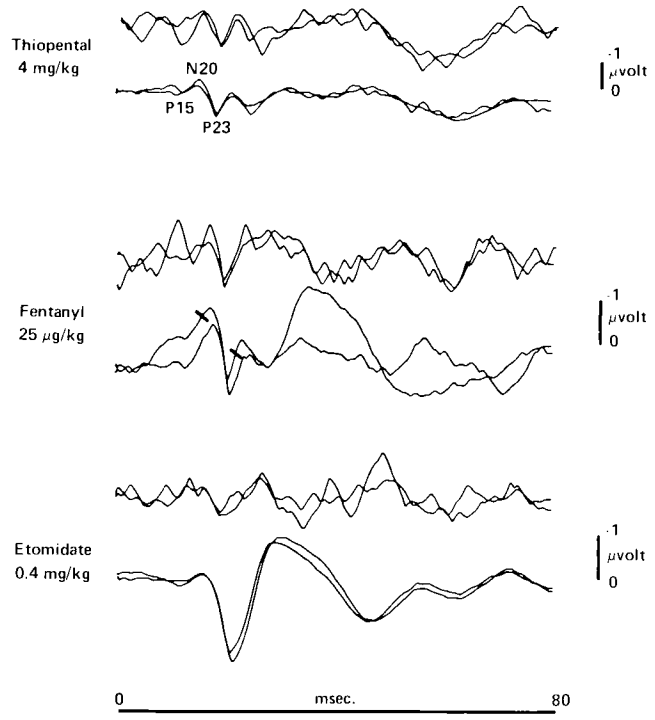

FIG. 1. Representative scalp recorded waves before and after anesthesia induction with thiopental (4 mg/kg), fentanyl (25 μg/kg), or etomidate (0.4 mg/kg) are shown. In the patient receiving fentanyl, the replicate wave is indicated by a *bar*.

latency of N20 and P23 without alteration of latency of N10, N14 or P15.

Figure 3 shows the amplitude of waves recorded at EP, SC-2 and contralateral scalp in Groups 1–3. Thiopental did not alter the amplitude at N10, N14 or scalp-recorded waves (P15–N20; N20–P23). Fentanyl decreased the amplitude of P15–N20 without alteration of N10, N14, or N20–P23. Etomidate decreased the amplitude of N14 without alteration of amplitude of N10. Amplitude of P15–N20 was increased to 140% of control, and N20–P23 was increased to 270% (range 150–400%) of control.

Table 2 shows the effect of propylene glycol (35%, iv bolus), the vehicle of etomidate, on SEP in neurologically normal volunteers. The vehicle had no effect on latency or amplitude of early SEP waves. Propylene glycol was injected into a rapidly flowing intravenous line, and no subject was aware of the time of injection. The volunteers were 29–37 yr of age (mean = 32 ± 2 yr) and were slightly taller than the patients (69 ± 2 in).

Discussion

Our data concerning the effects of thiopental, fentanyl, and etomidate on SEP have implications for intravenous drug administration during neurologic monitoring. First, clinically useful doses of fentanyl or thiopental produce only minor alterations in SEP. Second, etomidate dramatically increases scalp-recorded wave amplitude with lesser but significant changes in wave latency. The waveform changes caused by etomidate have implications concerning its use as an anesthetic induction agent, intravenous supplement during inhalational anesthesia, and in the head-injured patient if evoked-potential monitoring is being performed.

If etomidate is used as the induction agent, a variable period of instability of the SEP would occur for two reasons. First, the increased amplitude due to etomidate

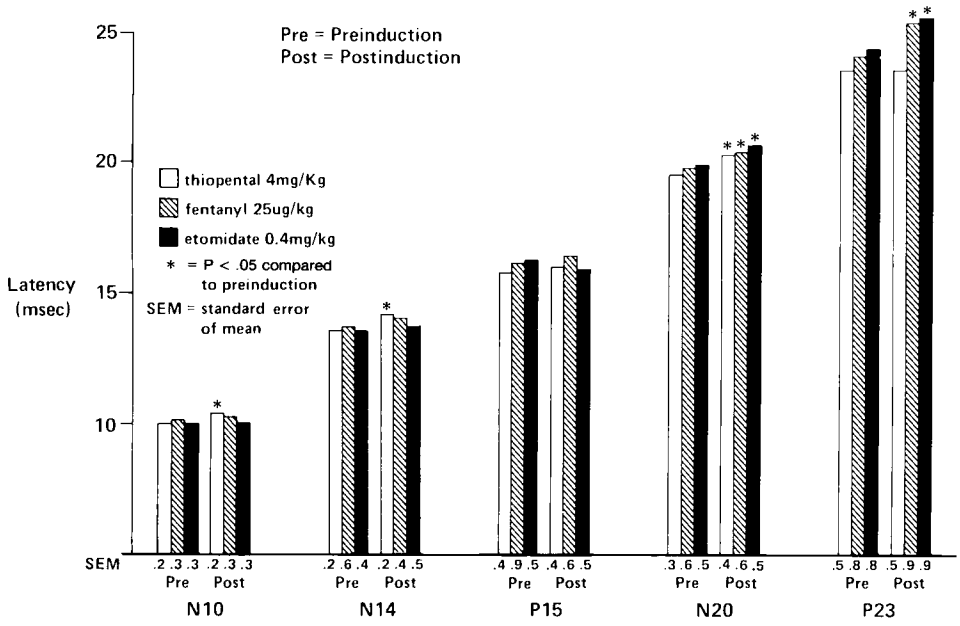

FIG. 2. The effect of thiopental (4 mg/kg), fentanyl (25 μg/kg), and etomidate (0.4 mg/kg) on latency at Erbs point (N10), second cervical vertebra (N14), and scalp-recorded waves P15, N20, and P23 are shown.

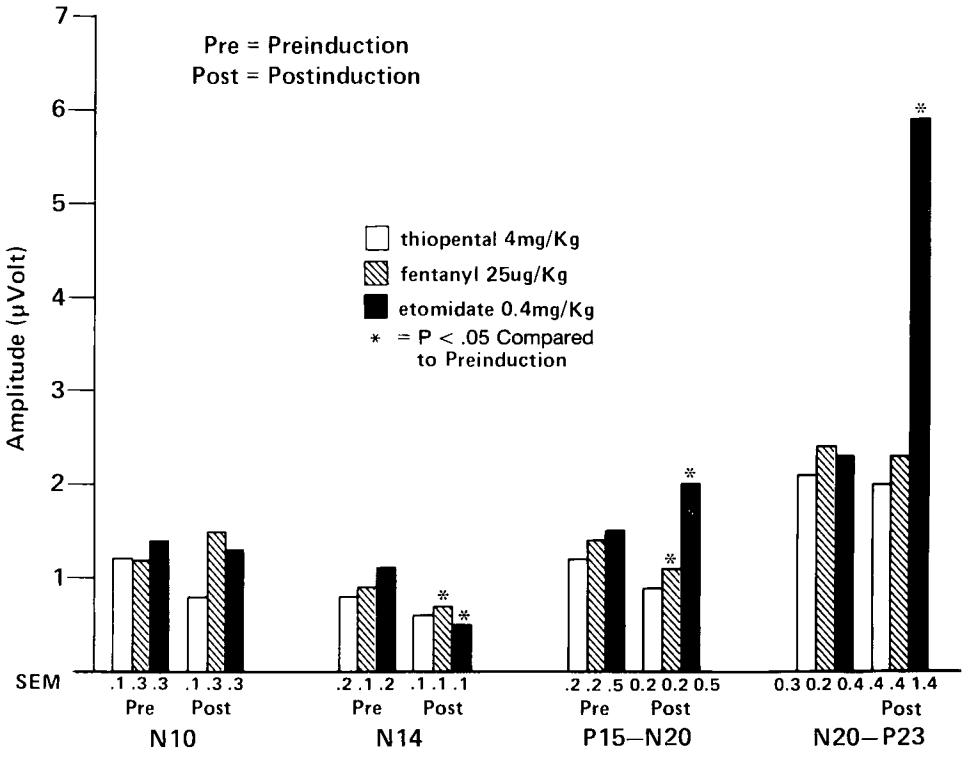

FIG. 3. The effects of thiopental (4 mg/kg), fentanyl (25 μg/kg), and etomidate (0.4 mg/kg) on amplitude of waves at Erbs point (N10), second cervical vertebra (N14), and scalp (P15–N20, N20–P23) are shown.

could be of short duration. Second, the addition of inhalational agents would be expected to depress the SEP.[6,9] Thus, the recorded waves would be rapidly decreasing in amplitude during a time in which the patient might be at risk of position-related neurologic injury.

In order to determine the effects of intravenous agents that alter the SEP on intraoperative monitoring, the changes in the SEP that indicate injury must be considered. A decrease in size (amplitude) and an increase in latency of SEP are commonly reported responses as neurologic tissue is deprived of oxygen.[10] However, there is some evidence to suggest that a transient increase in amplitude may be the initial response to oxygen deprivation.[11,12] This is suggested by the increased response of the cortex to direct stimulation during the onset of oxygen deprivation.[13] Because subcortical components are less sensitive to oxygen deprivation,[10,12] the situation exists early in oxygen deprivation in which the afferent volley from the thalamus would be normal but the cortex hyperpolarized, thus producing enhanced cortical waves. Thus, the increase in amplitude caused by etomidate may be mistaken for the onset of ischemia.

We must consider the agents studied for their usefulness as anesthesia induction agents in patients undergoing intraoperative SEP monitoring. Thiopental and etomidate both decrease cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMR_{O_2}),[14–16] properties that may be useful in preventing or minimizing neurologic injury. Fentanyl preserves cerebrovascular compensatory mechanisms such as autoregulation, responses to changes in Pa_{CO_2}, and cerebral oxygen deprivation.[17] Because none of the agents (thiopental, fentanyl, or etomidate) depressed SEP amplitude, all would seem appropriate for anesthesia induction, even in the presence of abnormally small SEP. A further consideration in intraoperative monitoring is the choice of intravenous agents to supplement anesthetic gases (for example, patient movement or cardiovascular response to stimulation). It would appear that thiopental or fentanyl would be preferable to etomidate, because amplitude changes caused by etomidate could make diagnosis difficult until the drug effect on SEP had dissipated. Cardiovascular stability with thiopental and etomidate in doses used in this study has been previously demonstrated.[18]

Because a neuromuscular blocking agent was administered in addition to the anesthetic induction agents, we must distinguish the effect of neuromuscular blockade from anesthetic drug effect. We have evidence from two sources that the effect of etomidate is unrelated to alteration in neuromuscular function. First, the same neuromuscular blocking agent was used in all groups, and the start point of each study (loss of consciousness) was similar. Second and more important, one patient (not included in study groups) received fentanyl on one occasion and etomidate on the other. The same neuromuscular blocking agent (pancuronium, 0.1 mg/kg) was used following

TABLE 2. Effects of 35% Propylene Glycol on SEP Amplitude and Latency Recorded at Erbs Point, Second Cervical Vertebra (SC-2), and Contralateral Cortex in Normal Volunteers (n = 6)

	Erbs Point		SC-2		Contralateral cortex				
					L			A	
	L	A	L	A	P15	N20	P23	P15–N20	N20–P23
Preinjection	10.2 ± 0.4	1.6 ± 0.2	13.4 ± 0.6	1.0 ± 0.3	15.5 ± 0.5	19.6 ± 0.7	22.8 ± 0.7	0.6 ± 0.1	1.4 ± 0.3
Postinjection	10.2 ± 0.3	1.7 ± 0.2	13.5 ± 0.7	0.9 ± 0.2	15.6 ± 0.6	19.3 ± 0.5	22.8 ± 0.5	0.8 ± 0.1	1.4 ± 0.3

Mean ± SEM. L = latency (ms); A = amplitude (μv).

both agents and quantitatively the results were similar to the other patients: no amplitude change with fentanyl and increased amplitude of waves P15–N20 and N20–P23 with etomidate.

Increased SEP amplitude in response to an anesthetic agent (trichloroethylene) has been previously reported.[19] In the example cited, the enhanced response was attributed to the motor response to stimulation. An increase in SEP amplitude has also been reported in a patient with sensory myoclonus.[20] Although etomidate has been associated with myoclonus,[21,22] the physical manifestation (muscle activity) was blunted or completely blocked by a neuromuscular blocking agent in this study. The lack of increased amplitude of N10 and N14 following etomidate when scalp-recorded waves increased dramatically (270%) suggests that the effect is cephalad to the spinal cord.

The reported effects of the agents, thiopental, fentanyl, and etomidate, on the electroencephalogram (EEG) do not offer a basis to explain the differential effect on scalp-recorded SEP waves. Thiopental (4 mg/kg) causes decreased fast-wave activity and slowing.[21] High doses of fentanyl (30 μg/kg) cause a decrease in frequency and an increase in amplitude.[23] The effect of etomidate (0.4 mg/kg) on EEG is similar to barbiturates with an increase in theta wave amplitude and slowing of alpha rhythm.[21,24] The lack of large effects of thiopental on recordings at EP, SC-2 and scalp-recorded waves demonstrated are consistent with other studies.[25] Likewise, the increased latency with fentanyl has been demonstrated previously in anesthetized patients.[26]

We investigated the vehicle of the preparation of etomidate used (Amidate®), 35% proplyene glycol, in a group of volunteers because central nervous system effects have been reported in high doses[27] and because it is the vehicle for other drugs (diazepam, phenytoin) that may either change central nervous system function or be administered in patients with central nervous system pathology. In the doses used (doses equal to that the subject would have received with 0.4 mg/kg of etomidate), there was no effect on the SEP.

We conclude that thiopental and fentanyl cause only minor alteration of upper extremity SEP, whereas etomidate results in a dramatic increase in scalp-recorded wave amplitude. This drug-induced alteration in SEP might interfere with determination of real change in neurologic function as assessed by the SEP, and the drug should be avoided during crucial periods of SEP monitoring. Because of lack of changes in peripherally recorded waves, we believe that this effect is central (above the level of spinal cord).

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