The Effects of Thiamylal Sodium on Electrical Activities of the Central and Peripheral Nervous Systems in Man

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The effects of thiamylal on the central and peripheral nervous systems of man were studied by simultaneous recording of somatosensory evoked responses from the scalp (SER), spinal epidural space (EESG), peripheral nerve (NAP) and muscle (EEMG). Clinical doses of thiamylal (2.5 mg/kg, 5 mg/kg) affect not only the SER but also the EESG and the H-reflex of the EEMG, without significant effect on the M-wave or NAP. Both early and late SER's were depressed in amplitude with prolongation of latency by the drug. The drug increased the amplitude of the N1 component of the EESG and prolonged P3-wave latency. Recovery of evoked responses after anesthesia was fastest with SER's and slowest with EEMG's. Thus, the changes caused by thiamylal in evoked responses in the peripheral and central nervous systems were not parallel in character or time course. (Key words: Anesthetics, intravenous: thiamylal; Brain: evoked responses; Brain: thiamylal; Nerve: thiamylal; Spinal cord: thiamylal.)

The somatosensory evoked response (SER) recorded from the scalp reflects the net results of neuronal activities coming from peripheral nerves through the spinal cord to the brain. In spite of this, effects of anesthetics on SER have generally been regarded as taking place within the brain. Clinical doses of anesthetics, however, affect not only the spinal cord but also peripheral nerves in man. For an appropriate approach to defining the anesthetic state, therefore, it would be necessary to analyze the effects of an anesthetic on the human nervous system as a whole. Simultaneous observations of activities in various parts of the nervous pathway might provide more valid information about fundamentals underlying the state of anesthesia. For this purpose, the present study was projected to determine the effects of thiamylal sodium on the SER, evoked electromyogram (EESG), nerve action potential (NAP), and evoked electromyogram (EEMG) in man by means of simultaneous recording.

Methods

Subjects were 15 patients free of neurologic deficit who underwent surgical operations under a combination of epidural and general anesthesia. Informed consent was obtained from all subjects. The study was performed in a quiet operating room during induction of anesthesia, before surgical manipulation was started.

The subjects lay first in the lateral decubitus position for placement of the electrodes, then supine for the observations. Venous cannulation was performed, and 5 per cent dextrose in water was administered at the rate of 15–30 drops/min throughout the experiment. All drugs were injected intravenously. Blood pressure was measured with a sphygmomanometer.

Chlorided silver needle electrodes were used for both stimulation and recording. In eight subjects, the posterior tibial nerve was stimulated at the popliteal fossa. The corresponding evoked electromyogram (EEMG) of the calf muscle, evoked electrospinogram (EESG) of T10–L1, and somatosensory evoked
response (SER) from the scalp at the vertex were recorded simultaneously. The technique of recording the EESG is described in a previous report.6

Both EEMG and NAP were recorded bипolarу, while EESG and SER were recorded monopolarу.

In seven subjects, the ulnar nerve was stimulated at the wrist. The EEMG of the hypothenar muscles, nerve action potential (NAP) of the ulnar nerve at the elbow, EESG at C5–C7, and SER from the scalp at C2P in response to ulnar-nerve stimulation were recorded simultaneously. C2P designated was located contralateral to the stimulated side and 2 cm posterior to a point 7 cm from the vertex on a line between the vertex and the ear.

The EEG and ESG were recorded by means of a four-channel polygraph (Nihon-Kohden RM-150 M), while NAP and EEMG were recorded on an oscilloscope (Nihon Kohden VC-7). All these potentials were also led to an FM magnetic tape and a computer (ATAC 501-10) for averaging either simultaneously or afterwards. The time constants used were 0.3 sec for EEG and ESG and 0.05 sec for EMG and NAP.

Electrical stimulation was delivered through a constant-current stimulator (Nihon Kohden MSE-3) with an isolation unit. Square-wave pulses of 0.5 msec duration, of sufficient intensity to produce hypothenar or calf twitch, occurred every 2–2.5 sec.

After preparation was complete, the subject was ventilated with oxygen through a well-fitted mask by a volume-preset respirator.
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Thiamylal, 2.5 mg/kg</th>
<th>Thiamylal, 5 mg/kg</th>
<th>Number of Subjects</th>
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</thead>
<tbody>
<tr>
<td>Somatosensory evoked responses from scalp</td>
<td></td>
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<tr>
<td>Early Latency</td>
<td>100 ± 1.4</td>
<td>104 ± 4.7</td>
<td>118 ± 3.6 (S)</td>
<td>13</td>
</tr>
<tr>
<td>Early Amplitude</td>
<td>100 ± 3.8</td>
<td>95 ± 6.1</td>
<td>79 ± 5.1 (S)</td>
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<td>Late Latency</td>
<td>100 ± 4.3</td>
<td>127 ± 7.2 (S)</td>
<td>131 ± 6.1 (S)</td>
<td>15</td>
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<tr>
<td>Late Amplitude</td>
<td>100 ± 11.2</td>
<td>41 ± 12.5 (S)</td>
<td>22 ± 14.0 (S)</td>
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<tr>
<td>Somatosensory evoked responses from epidural space (EESG)</td>
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<tr>
<td>N_1 Latency</td>
<td>100 ± 0.7</td>
<td>103 ± 4.8</td>
<td>102 ± 2.9</td>
<td>15</td>
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<tr>
<td>N_1 Amplitude</td>
<td>100 ± 2.3</td>
<td>135 ± 5.2 (S)</td>
<td>135 ± 4.3 (S)</td>
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<tr>
<td>P_2 Latency</td>
<td>100 ± 7.8</td>
<td>142 ± 6.3 (S)</td>
<td>149 ± 8.8 (S)</td>
<td>15</td>
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<tr>
<td>P_2 Amplitude</td>
<td>100 ± 9.1</td>
<td>128 ± 11.0</td>
<td>91 ± 13.3</td>
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<tr>
<td>Somatosensory evoked responses from muscle (EEMG)</td>
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<td>H-reflex Latency</td>
<td>100 ± 0.2</td>
<td>102 ± 3.0</td>
<td>102 ± 4.2</td>
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<tr>
<td>H-reflex Amplitude</td>
<td>100 ± 8.8</td>
<td>126 ± 9.1 (S)</td>
<td>41 ± 3.8 (S)</td>
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<tr>
<td>M-wave Latency</td>
<td>100 ± 0.2</td>
<td>99 ± 1.8</td>
<td>101 ± 2.0</td>
<td>14</td>
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<tr>
<td>M-wave Amplitude</td>
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<td>107 ± 5.8</td>
<td>98 ± 4.4</td>
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<tr>
<td>Somatosensory evoked responses from peripheral nerve (NAP)</td>
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<tr>
<td>Latency</td>
<td>100 ± 0.1</td>
<td>97 ± 4.3</td>
<td>98 ± 2.8</td>
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<tr>
<td>Amplitude</td>
<td>100 ± 0.3</td>
<td>101 ± 3.0</td>
<td>100 ± 0.7</td>
<td></td>
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<tr>
<td>Systolic pressure</td>
<td>100</td>
<td>93 ± 7.2</td>
<td>81 ± 4.7</td>
<td>15</td>
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* Means ± SE of maximum changes in averaged responses (n = 50) after drug administration were computed; 45–60 minutes elapsed between administration of the two doses.
† S, significantly different from control.

Tidal volume and respiratory rate were adjusted in reference to a Hadfield nomogram to avoid hypo- or hyperventilation, because the acid–base status strongly affects activities of the central and peripheral nervous systems.7 Arterial carbon dioxide tension (Paco₂) was monitored. Several minutes were allowed for the patient to become accustomed to the surroundings and to breathing with the respirator. While the patient rested quietly, with alpha waves predominating in EEG recordings, control recordings were made several times. Atropine, 0.5 mg, was injected immediately before administration of thiamylal. A single dose of 2.5 mg/kg thiamylal was injected intravenously within 10 sec. Thirty seconds after injection, recording of evoked activities was started. After recovery of evoked activities from administration of 2.5 mg/kg thiamylal (within 60 minutes), another 5 mg/kg thiamylal were injected and recordings were made sequentially.

Following the surgical procedures, subjects were taken to the recovery room, where the positions of the electrodes in the epidural space were verified radiologically.

**Results**

Figure 1 shows the effects of thiamylal, 5 mg/kg, on SER, EESG, NAP, and EEMG in response to ulnar-nerve stimulation in a sub-
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Figure 2. Left column, sequential changes in activities evoked in response to posterior-tibial-nerve stimulation after administration of thiamylal, 5 mg/kg. C, control (wakefulness). Time above each panel indicates the period during which averaging was done. Two averaged responses (n = 50) were obtained during each period; one during the first 100 sec (1), the other during the second 100 sec (2). Right column, strips of polygraphic records of the EEG and ECG. Beginnings of traces correspond to 120 sec (second panel) and 480 sec (third panel) after injection of the anesthetic.

As can be seen in this record, late SER's with latencies of more than 50 msec and responses later than the P2 component of the EEG were variable during wakefulness and anesthesia. The maximum changes in peak latency and peak amplitude of these activities evoked by the two doses of thiamylal are summarized in Table 1. It is clear from this table that increasing the dose of the drug produced pronounced changes in the variables measured. Latencies of both early and late SER's were prolonged by the anesthetic. Peak amplitudes of early as well as late SER's were decreased by the drug. These changes were more pronounced in late responses, with more variability. The amplitude of the N1 wave in the EEG was increased by the anesthetic without significant change in peak latency. Peak latency of the P2 component in the EEG was prolonged, while its peak amplitude was variable among the subjects (decreased in five and increased in three subjects). The amplitude of the H-reflex increased following 2.5 mg/kg of thiamylal but decreased following 5 mg/kg, without significant change in peak latency. The P1 wave, M-wave and NAP did not show any noticeable change throughout anesthesia.

Sequential changes in each evoked activity after administration of the drug were not uniform. Figure 2 shows a typical example of the periodic changes in evoked activities in response to posterior-tibial-nerve stimulation after injection of thiamylal, 5 mg/kg. Thirty to 230 sec after administration (fig. 2, second panel) both early and late SER's were depressed, with high-amplitude slow waves on the EEG. The N1 and P2 waves of the EEG increased in amplitude with simultaneous delays of their peak latencies. H-reflex amplitude decreased to 73 per cent of control. The M-wave remained constant during wakefulness and anesthesia.
Increase by about 20 per cent of control with 5 mg/kg (table 1). PaCO₂ did not change significantly throughout the study. PaCO₂ before induction, about 5 minutes after 2.5 mg/kg, and about 5 minutes after 5 mg/kg thiamylal were 38.4 ± 2.9 (mean ± SE), 37.6 ± 3.4, and 40.2 ± 1.2 torr, respectively.

Discussion

The purpose of the present study has been to detect a contribution of peripheral nervous system activity to SER’s affected by thiamylal anesthesia. Clinical doses of thiamylal affected not only SER’s but also the EESG and the H-reflex without significant effect on the M-wave or NAP in man. This indicates that thiamylal affects spinal as well as supraspinal nervous structures. Therefore, SER’s from any supraspinal level must be carefully analyzed, since they may reflect influences of changes in spinal levels by even clinical doses of thiamylal sodium. Unfortunately, it could not be confirmed in the present study how the modification of afferent inputs at spinal levels affects SER patterns.

The effects of barbiturates on human SER’s have been studied by several investigators. Although there are some discrepancies in the reported effects of anesthetics, overall depression of late SER’s by barbiturates seems to be a common finding. Slight depression of early SER’s by even clinical doses of thiamylal was found in the present study. This slight depression might or might not come from the blocking action of the anesthetic at the spinal level.

Reports concerning anesthetic effects on the EESG are scarce. Gasteiger and Ichikawa demonstrated uniform depression of the spontaneous activity of the electrospinogram (EESG) in the cat by ether and pentobarbital. In contrast, we have found some differential effects of anesthetics in human ESG’s and EESG’s.

The main changes in the EESG produced by thiamylal were the increase in N1 amplitude and the prolongation of P2 latency. Although the mechanism by which changes in the EESG influence SER patterns has not been clarified, our data indicate that anesthetic effects on somatosensory inputs at the spinal level modify SER patterns during anesthesia.

The origin of the N1 of the EESG of man has not been determined. However, the increase
in its amplitude with thiampyl suggests involvement of a presynaptic inhibitory component of the spinal cord, similar to the so-called "dorsal root potential" or "positive wave."\textsuperscript{14-15} Eccles et al.\textsuperscript{16} and Miyahara et al.\textsuperscript{17} reported the effect of thiopental on the monosynaptic spinal reflex of the cat. They postulated that the depression of the monosynaptic spinal reflex by anesthetics was the result of enhancement of presynaptic inhibition.

The variability of the P2 wave during wakefulness and anesthesia might result from the involvement of many neuronal origins in its production. The positive wave recorded from the cord dorsum of the cat, which is similar to the P2 wave in this study, was suggested by Gelfan and Tarlov\textsuperscript{18} to represent activity of the motoneuron pool, because of its close correlation with the monosynaptic reflex. However, we could not confirm a rigorous correlation between the amplitude changes in the P2 wave and those in the H-reflex caused by the anesthetic. The prolongation of the peak latency of the P2 wave by the anesthetic in the present study was more empirical change. Susceptibility of its latency to the anesthetic also suggests that postsynaptic potentials are the major elements in production of the P2 wave.\textsuperscript{19}

The changes in the EEMG in the present study coincide with our previous findings in man.\textsuperscript{2} The effect of barbiturates on the spinal monosynaptic reflex (MSR) has been studied in decerebrate cats.\textsuperscript{16,17,20,21} Although Eccles et al.\textsuperscript{16} and Layning et al.\textsuperscript{21} observed a similar blocking effect of barbiturates on the MSR, there has been some controversy about the cause of the block; various investigators have proposed blockade of excitatory postsynaptic potentials,\textsuperscript{22,23} depression of afferent nerve terminals,\textsuperscript{21} and enhancement of presynaptic inhibition.\textsuperscript{16-17} Enhancement of MSR with a small dose of barbiturates has been found not in work in spinal cats.\textsuperscript{2} Therefore, differences in changes of H-reflex amplitude in relation to dose might be due in part to supraspinal influences. It is well known that there are inhibitory as well as excitatory influences of supraspinal structures on the MSR. A small dose of thiampyl might block inhibitory influences, resulting in excitatory effects on the MSR.\textsuperscript{2}

The increments or decrements of the various evoked activities after drug injection did not have the same time course. More rapid recovery of SER's affected by the anesthetic might be attributed to the rich blood supply and high metabolic rate of the brain.\textsuperscript{24} Another factor which governs the differences in time course changes among evoked activities might be differential effects of the anesthetic on the afferent sensory and the efferent motor systems.\textsuperscript{25} Insignificant changes in NAP and the M-wave in this study confirm our previous findings\textsuperscript{2} that thiampyl, at least in clinical doses, does not act on peripheral nerve conduction and neuromuscular transmission in man.

The authors thank Dr. Joseph M. Messick, Jr., for assistance in preparing the manuscript, and Drs. Arthur S. Keats and T. Morioka for their valuable criticism.

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Circulation

HEMODYNAMIC EFFECT OF CAN-
GLION BLOCKERS The effects of an
fusion of trimethaphan camyslate (Arfonad) and the associated reduction of afterload on left ventricular performance were studied in 13 patients within 6 hours of the end of an intraaortic operation requiring cardiopulmonary bypass. The patients were selected because their mean aortic pressures (MAP) were greater than 100 mm Hg. Arfonad was infused at a rate of 2 to 4 mg/min to reduce MAP an average of 24 mm Hg and to maintain it at that level. Heart rate (HR) was essentially constant in every patient throughout the study. In five patients with mean left atrial pressures (MLAP) below 15 mm Hg (mean ± SD = 10 ± 3 mm Hg) and elevated MAP’s (139 ± 10 mm Hg), mean cardiac index (Cl) was 2.78 ± 0.8 l/min/m². Infusion of Arfonad in these patients produced decreases in MAP which averaged 31 mm Hg. Associated with these decreases in MLAP (40 per cent), stroke index (SI) (18 per cent), and left ventricular stroke work index (LVSWI) (35 per cent). CI decreased 16 per cent, which was not significant. Mean right atrial pressure (MRAP), HR and peripheral vascular resistance did not change significantly.

In the eight patients with initial MLAP’s greater than 15 mm Hg (mean 25 ± 5 mm Hg) and elevated MAP’s (109 ± 6 mm Hg), CI was considerably lower (1.76 ± 0.3 l/min/m²). Infusion of Arfonad in these patients resulted in significant reductions in MAP (mean 19 mm Hg) and a 36 per cent reduction in MLAP. Associated with this were significant increases in SI (18 per cent) and CI (15 per cent) and significant decreases in MRAP and PVR. HR and LVSWI did not change significantly. (Kouchoukos, N., Sheppard, L. C., and Kirklin, J. W.: Effect of Alterations in Arterial Pressure on Cardiac Performance Early after Open Intracardiac Operations. J. Thorac. Cardiovasc. Surg. 64:563-572, 1972.)