The effects of deep barbiturate coma on multimodality evoked potentials

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The authors report their investigation of the effects of high-dose barbiturates on the multimodality evoked response in 9 cats. After baseline evoked responses were obtained, boluses of pentobarbital were infused intravenously at regular intervals, amounting to cumulative total doses of 9, 18, 27, 45, 63, 123, and 183 mg/kg at respective infusions. This resulted in gradually increasing serum pentobarbital levels, reaching therapeutic coma levels (4 to 5 mg/dl) after the fifth infusion. At this point, the electroencephalogram was flat, and pressor agents were required to maintain cardiovascular stability. Evoked responses were obtained 15 minutes after each infusion. Brain-stem auditory evoked response (BAER) showed little change in wave latencies at therapeutic coma levels of pentobarbital. Further barbiturates resulted in delay of the late components of this response. In the somatosensory evoked responses (SER), early brain-stem components were relatively unaffected by therapeutic coma levels. Late brain-stem components and the initial cortical response showed progressive latency increase. Late cortical (association cortex) waves were abolished at relatively low doses. The central conduction time was relatively unaffected. The late waves of the visual evoked responses (VER) were abolished with low-dose barbiturates (9 mg/kg). A single positive-negative complex persisted despite massive infusions. It is concluded that evoked responses may prove useful in monitoring patients in deep barbiturate coma, but barbiturate effects must be kept in mind.

KEY WORDS: evoked response, brain stem, barbiturate, coma, multimodality evoked response

Iatrogenic barbiturate coma has been employed increasingly in an attempt to protect the brain from a variety of insults, including head injury,7,20 Reye's syndrome,8 and cerebral ischemia due to vascular occlusion.5,18 A drawback of this therapy is that the physician loses all of the traditional methods of assessing neurological integrity: in deep barbiturate coma, the brain-stem reflexes disappear, and even the electroencephalogram (EEG) becomes isoelectric. One is then totally dependent on intracranial pressure (ICP) monitoring in determining when to alter treatment.

Multimodality evoked potentials (MEP), a battery consisting of the visual evoked response in response to a strobe flash (VER), the somatosensory evoked response (SER), and the brain-stem auditory evoked response (BAER), might offer a means of objective assessment of a variety of brain pathways if they remained present in the face of deep barbiturate coma. Most of the work done relating evoked responses to barbiturates has focused on relatively low (anticonvulsant) doses.2,5,13,17 The usefulness of the various components of the MEP as a monitoring technique in deep barbiturate coma is yet to be established.

In addition to their potential usefulness as a means of monitoring patients, MEP have shown promise as a means of determining prognosis, particularly in head injury,19,21,22 cerebral ischemia,6,27 and coma of multiple etiologies.13 These are the disease processes in which iatrogenic barbiturate coma is likely to be used, and it is, therefore, vital to separate the effects of barbiturate on the MEP from those of the underlying disease process if useful prognostication is to be achieved.

We examined the effects of large doses of pentobarbital, sufficient to produce coma, on the MEP in cats. We chose to initially study these effects in animals so that factors known to affect the recordings.
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(such as blood pressure, temperature, and underlying disease), so variable in the clinical setting, could be rigidly controlled.

Materials and Methods

Animal Preparation

Nine female cats, weighing 2.5 to 3.5 kg with initial hematocrits greater than 30%, were studied. Animals were anesthetized with ketamine, 75 to 150 mg given by intraperitoneal injection. A peripheral vein was cannulated, and atropine (0.2 mg) administered. All cats were then intubated after 3 minutes of preoxygenation by mask. Neuromuscular blockade was induced with pancuronium (0.1 mg/kg). Ventilation with 30% oxygen was then adjusted to maintain end-tidal CO₂ between 30 and 36 torr. Rectal temperature was kept between 38.5° and 39.5°C.

A femoral artery and vein were cannulated using the Seldinger technique. The systemic mean arterial pressure (SMAP) was maintained between 130 and 160 torr. This was achieved initially by using crystalloid boluses, with dopamine HC₁ infusions required in the later stages of the experiment. Urine output was greater than 1 ml/kg/hr throughout. Arterial blood gases were measured every 4 hours. Arterial pH was corrected to 7.37 with NaHCO₃ when necessary. The PaO₂ was greater than 150 torr on all measurements.

Recording Procedures

The MEP comprised short- and long-latency visual and somatosensory evoked responses (VER, SER), and brain-stem auditory evoked responses (BAER). In preparation for recording, the animals were placed in a stereotaxic headholder equipped with a hollow ear bar on the side that was to receive auditory stimulation. (The solid contralateral ear bar attenuated the sounds associated with the visual stimulator and other apparatus). Because correct placement of the hollow ear bar is difficult in the cat, which has a tortuous ear canal, positioning was verified by visual examination using a small light source. The scalp was incised along the midline and retracted. Three stainless steel epidural bolt electrodes were placed: an occipital electrode for VER was inserted just off the midline at the level of the insertion of the occipital muscles, a parietal electrode for SER was placed 7 mm posterior to the coronal suture and 1 cm lateral to the midline contralateral to the stimulus, and a nasofrontal electrode was placed as a reference over the frontal sinus. Needle electrodes were inserted over the bullae of both ears.

The VER were elicited by strobe flashes at a rate of 2/sec delivered by a Grass photostimulator,* with the flash unit at maximal intensity and placed 20 cm in front of the eyes. The response was recorded from the occipital electrode, referenced to the frontal electrode. The former was the negative and the latter the positive input to a Grass P511 preamplifier,† which had a ground connection to the needle electrode over one bulla. After amplification with a Grass P5 amplifier;‡ (gain of 50,000, 3Hz-2 kHz bandpass), 256 responses were summed on an Apple II plus computer equipped with an analog-to-digital converter, and digitally plotted so that a positive potential applied to the occipital electrode resulted in an upward deflection. A time scale of 150 msec was used (50 msec prestimulus data) with a sampling rate of 256 points/sweep.

The stimulus for the SER was a 5-volt, 0.2-msec square-wave shock delivered via two needle electrodes inserted near the median nerve at a rate of 2/sec. The response was recorded from the contralateral parietal electrode referenced to the frontal electrode and amplified (gain 50,000, 3Hz-3 kHz bandpass). After 256 responses were averaged, the response was plotted so that a positive potential applied to the parietal electrode resulted in an upward deflection. Both 30- and 150-msec sweep times were used so that long- and short-latency components could be analyzed. For brain-stem and cortical components, the temporal resolution was 0.15 msec and 0.78 msec, respectively.

The BAER stimulus was a click generated by delivering a 100-μsec square-wave pulse to a TDH-39 earphone that was coupled to the hollow earbar via an otoscope speculum. The stimulus was delivered at an intensity 60 dB above the animal's BAER threshold, at a rate of 20/sec. The responses to 1024 compression and 1024 rarefaction clicks were added together with an analysis time of 10.24 msec, and a temporal resolution of 20 μsec. For this response, the frontal electrode was positive with respect to the needle electrode over the bulla of the stimulated ear, with the contralateral bulla electrode serving as ground; frontal-positive potentials are represented as upward deflections. Preamplifier gain was 50,000, with a bandpass of 10 Hz-3 kHz.

A one-channel EEG was recorded from the frontal and occipital epidural electrode bolts, using one of the needle electrodes in the ear as a ground. The signal was amplified by a Van Gogh amplifier§ (time constant 0.15) so that a 50-μV pulse resulted in a 1-cm pen deflection.

Experimental Design

The VER, SER, BAER, and EEG were monitored before treatment to determine a baseline and, again, 15 minutes after the end of each pentobarbital infu-

* Photostimulator manufactured by Grass Instrument Co., 101 Old Colony Avenue, Quincy, Massachusetts.
† Grass P511 preamplifier manufactured by Grass Instrument Co., 101 Old Colony Avenue, Quincy, Massachusetts.
‡ Grass P5 amplifier manufactured by Grass Instrument Co., 101 Old Colony Avenue, Quincy, Massachusetts.
§ Van Gogh amplifier manufactured by Ahrend-Van Gogh Co., Amsterdam, The Netherlands.
FIG. 1. Mean serum pentobarbital level and standard deviation in relation to cumulative dose infused. Samples were drawn 15 minutes after termination of each of five infusions. A linear relationship was obtained, plotted by linear regression analysis ($r = 0.9$).

FIG. 2. Electroencephalogram (EEG) recording from an occipital epidural electrode, referenced to a frontal sinus indifferent electrode. A: Baseline; B: Following 9 mg/kg infusion of pentobarbital; C: Following an additional 9 mg/kg (total dose 18 mg/kg); D: Burst-suppression is evident at a total dose of 27 mg/kg; E: Random spikes are seen at a total dose of 45 mg/kg; F: Isoelectric EEG at total dose of 63 mg/kg. In this figure, full-scale pen deflection is 125 $\mu$V.

Data Analysis

When inadequate baseline evoked responses were obtained, that modality was not analyzed for that particular animal. Thus, the data from six animals were analyzed for VER, from seven for SER, and from six for BAER.

Latencies for selected waves were measured graphically from stimulus onset to wave peak. Wave identification was occasionally difficult after the pentobarbital infusions had begun, but clarification was aided by superimposing serial traces and by following the progression of abnormalities as the cumulative dose increased.

Wave amplitudes were not analyzed, as they are so variable, even in normal populations, that their clinical significance is doubtful. The disappearance of a wave in one-half or more of the subjects was considered significant, and was the criterion for reporting a wave as abolished. The latencies of these waves that persisted after each barbiturate infusion were recorded and compared with baseline latencies for that animal, using the paired t-test.

Results

Pentobarbital Levels

The infusion of pentobarbital resulted in gradually increasing serum levels (Fig. 1). By the end of the fifth infusion, all animals had reached levels considered desirable in human patients. In the two animals given infusions totaling 183 mg/kg, the barbiturate levels were 9 mg/dl and 11 mg/dl.

Electroencephalogram

The typical changes induced by progressive barbiturate loading are demonstrated in Fig. 2. Little change was noted following the first infusion. After the second infusion, some animals showed an increase in high-frequency activity, but most were unchanged. The third infusion resulted in burst-suppression activity in most animals, and by the end of the fourth and fifth infusions the animals showed very low voltage activity with occasional spikes or isoelectric traces.

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Harvard infusion pump manufactured by Harvard Apparatus Co., 150 Dover Road, Millis, Massachusetts.
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TABLE 1

<table>
<thead>
<tr>
<th>Pentobarbital (mg/kg)</th>
<th>P1</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
<th>P3</th>
<th>N3</th>
<th>P4</th>
</tr>
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<tr>
<td>0</td>
<td>12.03 ± 1.13</td>
<td>18.10 ± 2.11</td>
<td>27.6 ± 2.9</td>
<td>32.7 ± 2.5</td>
<td>40.2 ± 5.0</td>
<td>46.9 ± 3.8</td>
<td>58.0 ± 4.9</td>
</tr>
<tr>
<td>9</td>
<td>13.28 ± 2.04</td>
<td>23.63 ± 3.02</td>
<td>–</td>
<td>–</td>
<td>50.3 ± 8.8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>13.57 ± 1.74</td>
<td>25.23 ± 4.38</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>27</td>
<td>14.12 ± 2.34</td>
<td>25.43 ± 4.50</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>45</td>
<td>14.20 ± 1.90</td>
<td>24.10 ± 5.38</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>63</td>
<td>13.28 ± 0.69</td>
<td>21.75 ± 1.29</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Waves are given as mean (msec) ± standard deviation for six animals. Pentobarbital infusion is given as the cumulative dose.
† Significantly different from baseline: paired t-test, p < 0.05.

Visual Evoked Response

In the control period, seven waves were consistently identified within 150 msec, the period of post-stimulus data recording. These waves were similar to those reported previously by Greenberg, et al., with some latency differences attributed to slightly different stimulus and recording parameters. Following their nomenclature, these waves were designated P1, N1, P2, N2, P3, N3, and P4. The latencies of these VER waves are presented in Table 1, with a representative series of VER's from a single animal in Fig. 3.

After the administration of 9 mg/kg of pentobarbital, a significantly increased latency of wave N1, as compared to baseline, was noted (p < 0.05), and waves P2, N2, P3, N3, and P4 were abolished. Only P1 and P2 did not significantly change in latency after the first dose. After a total of 27 mg/kg of pentobarbital, the latency of wave P1 was significantly prolonged relative to baseline, but still discernible. Waves P2 and N2 persisted through all five doses of pentobarbital, despite a flat EEG, and even in the two cats with pentobarbital concentrations exceeding 9 mg/dl.

Somatosensory Evoked Response

Baseline SER were obtained for both early (< 10 msec) and late (10 to 150 msec) components. Latencies for positive early components were in good agreement with those of Wiederholt, Iragui-Madoz and Wiederholt, and others. These waves, thought to arise from brain-stem structures, were designated I, II, III, and IV following the nomenclature of previous authors. Latencies of later cortical components were in agreement with previous reports and were designated P1, N1, P2, and N2 (Table 2). The central conduction time was calculated for each animal by subtracting the latency of Wave II (thought to arise from the medial lemniscus and nucleus cuneatus) from the latency of the first cortical potential (P1).

As with the VER, the long-latency components of the SER were those most easily affected by pentobarbital (Fig. 4). With infusion of the first 9 mg/kg, a significant increase in latency was seen in the late cortical waves (P2, N2). The waves disappeared by the end of the third infusion. The primary cortical response (P1, N1) persisted throughout the experiment, but progressively increased in latency. This primary response persisted even in the two animals in which it was possible to infuse 183 mg/kg of pentobarbital, but it was quite attenuated.
TABLE 2

Somatosensory evoked response: average latency of selected brain-stem and cortical peaks before and after infusions of pentobarbital*

<table>
<thead>
<tr>
<th>Pentobarbital (mg/kg)</th>
<th>Brain-Stem Peaks</th>
<th>Cortical Peaks</th>
<th>CCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>0</td>
<td>3.6 ± 20</td>
<td>5.20 ± 20</td>
<td>6.71 ± .38</td>
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<tr>
<td>9</td>
<td>3.82 ± 16</td>
<td>5.31 ± 15</td>
<td>6.94 ± .55</td>
</tr>
<tr>
<td>18</td>
<td>3.86 ± 23</td>
<td>5.53 ± 17†</td>
<td>7.26 ± .52†</td>
</tr>
<tr>
<td>27</td>
<td>3.82 ± 25</td>
<td>5.45 ± 27†</td>
<td>7.36 ± .34†</td>
</tr>
<tr>
<td>45</td>
<td>3.88 ± 26</td>
<td>5.47 ± 27†</td>
<td>7.51 ± .30†</td>
</tr>
<tr>
<td>63</td>
<td>3.97 ± 20†</td>
<td>5.72 ± 22†</td>
<td>7.60 ± .21†</td>
</tr>
</tbody>
</table>

* Peaks are given as mean (msec) ± standard deviation for seven animals. Pentobarbital infusion is given as the cumulative dose.
† Statistically different from baseline: paired t-test, p < 0.05.

The brain-stem waves were affected relatively later than the cortical waves. The later brain-stem waves (II, III, IV) were affected relatively earlier than the first component (I), although by the end of the fifth infusion all components of the SER had shifted significantly (Fig. 5).

Central conduction time showed a gradual tendency to increase with increasing barbiturate dose, but this change failed to reach statistical significance.

Brain-Stem Auditory Evoked Response

Four well-defined frontal positive waves (designated I to IV) were analyzed within the first 5 msec after the stimulus (Table 3). These are similar to those obtained by other authors14,16 and arise from cochlear nerve and brain-stem structures.1,10,11 The latencies of the BAER in six animals are listed in Table 3. An illustration of a series of responses from a single animal is presented in Fig. 6.

The BAER proved remarkably resistant to barbiturate effects. Although a steady small increase in latency was seen in all waves with increasing pentobarbitol.
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BARBITURATE EFFECTS ON THE LATE CORTICALLY DERIVED WAVES OF THE SER WERE SIMILAR. LOW-DOSE PENTOBARBITAL RESULTED IN PROLON- GATION AND EVENTUAL LOSS OF THESE COMPONENTS. AFTER PENTOBARBITAL CONCENTRATIONS REACHED THE THERAPEUTIC RANGE, THE REMAINING COMPONENTS OF THE SER, INCLUDING THE PRIMARY CORTICAL RESPONSE AND WAVES OF BRAIN-STEM ORIGIN, WERE SIGNIFICANTLY DELAYED, BUT EARLY COMPONENTS DID PERSIST. THEREFORE, IT WOULD APPEAR THAT THE SER MAY STILL BE USEFUL, AT LEAST IN A QUALITATIVE WAY, AS AN INDEX OF BRAIN-STEM AND PRIMARY CORTEX ACTIVITY. THE CENTRAL CONDUCTION TIME DID NOT SIGNIFICANTLY CHANGE WITH INCREASING BARBITURATE DOSAGE. CENTRAL CONDUCTION TIME HAS BEEN SHOWN TO BE A SENSITIVE INDEX OF CEREBRAL ISCHEMIA BOTH IN THE CAT24 AND IN MAN,26 AND IT IS POSSIBLE THAT IT COULD RETAIN ITS USEFULNESS IN THIS WAY DESPITE THERAPEUTIC BARBITURATE COMA.

The brain-stem components of the auditory evoked response proved remarkably resistant to barbiturate effects. Even with massive doses and enormous serum barbiturate dosage, this did not become statistically significant until 63 mg/kg had been infused, and even then only Waves III and IV were significantly delayed. Although all changes in the BAER were small, the findings were similar to those seen with the VER and the SER, in that later waves demonstrated a larger latency increase than earlier ones.

Discussion
Evoked responses are often considered to be independent of anesthetic dose13 and, with relatively small barbiturate doses, this seems to be true. Normal anticonvulsant levels of phenobarbital (0.1 to 0.25 mg/dl) have been shown to have no effect on the SER in cats.17 However, with toxic levels (greater than 0.25 mg/dl), amplitude changes have been reported.2,17 Other authors have noted latency increases of late components of the SER with light barbiturate anesthesia.2,3

Our study examined the effects of high barbiturate doses on MEP. We chose to initially study these effects in cats so we could directly attribute the recordings obtained to the doses of barbiturate given. The doses employed produced an isoelectric EEG and serum concentrations similar to or greater than those encountered in the treatment of brain-injured patients. Pentobarbital was given in serial boluses so that the effects of increasing doses on the MEP could be determined.

The earliest effect seen on the VER was a loss of the long-latency (greater than 20 msec) components, which occurred after only 9 mg/kg of pentobarbital had been given. Further infusions resulted in prolongation of earlier waves, but even after large doses and a flat EEG the earliest waves did not entirely disappear. The persistence of the early VER waves suggests that the VER may prove useful in monitoring human brain function under barbiturate coma, if, in fact, the N2 wave in the cat is cerebral in origin. Further study of the origins of these waves will be necessary before their clinical value can be confirmed.

Barbiturate effects on the late cortically derived waves of the SER were similar. Low-dose pentobarbital resulted in prolongation and eventual loss of these components. After pentobarbital concentrations reached the therapeutic range, the remaining components of the SER, including the primary cortical response and waves of brain-stem origin, were significantly delayed, but early components did persist. Therefore, it would appear that the SER may still be useful, at least in a qualitative way, as an index of brain-stem and primary cortical activity. The central conduction time did not significantly change with increasing barbiturate dosage. Central conduction time has been shown to be a sensitive index of cerebral ischemia both in the cat24 and in man,26 and it is possible that it could retain its usefulness in this way despite therapeutic barbiturate coma.

The brain-stem components of the auditory evoked response proved remarkably resistant to barbiturate effects. Even with massive doses and enormous serum
levels of pentobarbital, all four components persisted, although increases in latency were noted. We have noted similar findings in a limited number of human subjects in deep barbiturate coma, and it is likely that the BAER will prove useful in assessing brain-stem integrity in therapeutic coma.

The mechanism of action of the barbiturates is not entirely understood. However, it is generally believed that the synapse is the site of action of hypnotic compounds. Our finding that the late components of the MEP (which arise from polysynaptic cortical association areas) are the most sensitive to pentobarbital, and that the short-latency (end organ and brain-stem) components are resistant, supports this hypothesis, in that one would anticipate a cumulative barbiturate effect to magnify over a polysynaptic pathway.

In summary, we have studied the effects of barbiturates on MEP and found that, in general, early components persisted even in the presence of large serum pentobarbital concentrations and an isoelectric EEG. However, some late components of the MEP were abolished even at low serum pentobarbital concentrations. Our data suggest that the presence or absence of MEP waves will prove useful in the assessment of the brain stem and cortex even in the presence of barbiturate coma, but that changes in latency do occur.

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References

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