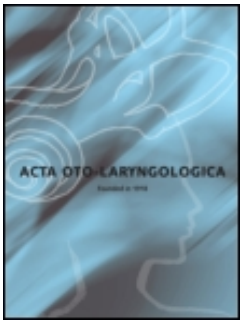

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The Effects of High-dose Barbiturates on the Acoustic Reflex and Auditory Evoked Responses

Two Case Reports

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The effects of high-dose barbiturates (pentobarbital) on the acoustic reflex, and the auditory brainstem (ABR) and middle-latency (AMR) responses, are illustrated with two case reports. Auditory electrophysiologic data were recorded serially during recovery from therapeutic barbiturate coma. ABR latency remained within normal limits in barbiturate coma, but amplitude of the wave I component was abnormally augmented. Contralateral and ipsilateral acoustic reflex activity, and the Pa component of the AMR, were not observed in barbiturate coma, and reappeared with the emergence of brainstem neurologic signs. These findings suggest a fundamental difference in the neurophysiologic substrate of the ABR vs. acoustic reflex and AMR. Possible mechanisms for the differential influence of barbiturates on these three auditory electrophysiologic measures are offered. *Key words: auditory brainstem response, auditory evoked potentials, auditory middle-latency response, brain injury, coma, head injury, intracranial pressure, reticular formation.*

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There is experimental evidence that anesthetic doses of pentobarbital (Nembutal) reduce acoustic middle ear reflex activity (1–3) and suppress or abolish auditory evoked responses (AER's) in the middle-latency (20 to 100 msec) region (4–8). In contrast, the auditory brainstem response (ABR) in animal, at least cat and rat, is extremely resistant to the effect of barbiturates (9–13).

Clinical investigations of the influence of barbiturates on the acoustic reflex and AER's are scarce and with few exceptions limited to light anesthetic doses of the drug. Pentobarbital is a short-acting anesthetic agent that appears to effect the central nervous system (CNS) by depressing the ascending reticular activating system (RAS) in the brainstem (14). Large doses of pentobarbital lead to coma and, by depressing brainstem respiratory centers and reducing CNS responsiveness to blood gas alterations, can be lethal. Barbiturates in doses of up to 4 mg/kg decrease sensitivity of the acoustic reflex in man (15–17). That is, increased stimulus intensity levels are required to elicit the aoustic reflex. The effect of barbiturates appears to be more pronounced on the contralateral, or crossed, acoustic reflex pathways and may be greater in humans than animal models (2, 16).

Starr & Achor (18) reported normal ABR findings for four patients in coma following an overdose of barbiturates. Clinical neurologic signs were suppressed. In a recent clinical study, Newlon and colleagues (19) compared ABR latency values for a group of 15 head-injured patients in therapeutic barbiturate coma and a control group of 12 patients with equivalent neurologic status, but not receiving barbiturates. These investigators concluded that the ABR was not significantly altered by barbiturates. The study, however, was characterized by at least four methodologic limitations that appear virtually unavoidable when a group experimental design is used to clinically assess the influence of barbiturates

on evoked responses. First, serum barbiturate levels were relatively low (11 to 35 μg/ml range, with a mean level of 19 μg/ml). Second, 95% of the treatment group and 94% of the control group initially yielded abnormal findings in a multimodality evoked response battery, which included the ABR. Third, 60% of the treatment group was hypothermic at the time of the study, yet all patients in the control group were normothermic. There is an established relationship between body temperature and the ABR (20, 21). Finally, ABR latency data were highly variable within each group. Amplitude data were not analyzed. The outcome of the study by Newlon and colleagues does not, therefore, conclusively confirm clinically the influence of barbiturates on the ABR. And, to our knowledge, there are no published clinical reports describing the relationship between barbiturates and the auditory middle-latency response (AMR).

In this paper, we present two case reports to illustrate the differential effect of high dose barbiturates on serial measures of the acoustic reflex, auditory brainstem response and middle-latency (AMR) response in man.

METHODS

Acoustic reflex data were collected with a commercially-available instrument (Amplaid 702). An immittance test battery was administered according to standard clinical protocol (22), and included tympanometry and measurement of static compliance and the acoustic reflex for each ear. Contralateral and ipsilateral acoustic reflexes were activated by pure-tone stimuli (octave frequencies of 500 through 4000 Hz) and broad-band noise, presented via a TDH-49 earphone coupled to a MX-41/AR cushion (contralateral) or a miniature transducer seated within the immittance probe assembly (ipsilateral). Acoustic reflex thresholds, approximated in 5 dB increments, were defined as the lowest stimulus intensity level producing a reliable change in immittance as detected visually on a graphic display. Maximum signal intensity level for acoustic reflex thresholds measurement was 110 dB (HL).

Auditory evoked responses were stimulated, measured and analyzed at bedside in a surgical intensive care unit (SICU) with a clinical evoked potential system (Nicolet CA-1000/DC-2000). The stimuli were clicks of 0.1 msec duration presented with standard audiometric earphones (TDH-39) at an intensity level of 85 dB (Re: normal click hearing level, NHL) and at a rate of 21.1/sec (ABR) or 11.1/sec (AMR). The neural signal was detected with gold, disc-type electrodes (forehead positive, earlobe negative), amplified (×100000) and then filtered (150 to 3000 Hz, ABR; 30 to 100 Hz, AMR). Interelectrode resistance was always less than 5000 Hz. Response latency and amplitude values were determined for the sum of two waveforms, each averaged for a total of 2000 stimuli (ABR) or 1000 stimuli (AMR). Acoustic reflex and auditory evoked response data were obtained and analyzed without prior knowledge of barbiturate blood levels.

RESULTS

Case 1

The patient was a 38-year-old male sustaining a severe cerebrovascular insult secondary to heart-lung machine complications encountered during a double coronary artery bypass operation at an outlying hospital. He was immediately transferred to the Hospital of the University of Pennsylvania. Upon arrival, pupils were pinpoint and appeared unreactive bilaterally. Painful stimulation produced eye opening and a localizing motor response on the left, but no movement of extremities on the right. Computerized tomography (CT)

revealed left hemisphere brain swelling and a mild left-to-right shift. The patient was taken to the SICU. An intracranial pressure (ICP) monitor (Richmond bolt) was placed, with an opening pressure of 65 cmH_2O. Following a 50 g bolus of a hyperosmolar drug (Mannitol), ICP decreased to 20 mmHg. High-dose barbiturate therapy was then initiated with a 200 mg bolus of Nembutal, and maintained by infusion.

Acoustic reflex and AER measurements were initially made on the first post injury day. Serial physiologic, neurologic and AER data are summarized in Table I. Barbiturate blood level reached a maximum of 36 μg/ml, and was then gradually tapered over a period of 104 hours. Physiologic parameters (body temperature, blood gases, ICP, mean arterial pressure, cerebral perfusion pressure) were stable throughout barbiturate coma. Clinical neurologic signs were initially not observed, and then emerged as the barbiturate blood level decreased. The ABR was consistently recorded in barbiturate coma (see Fig. 1). Latency and amplitude values remained well within our normative region. The AMR and acoustic reflex, in contrast, were not observed in deep barbiturate coma (see Figs. 1 and 2). The Pa component of the AMR was first recorded at the test session coinciding with the finding of pupillary reactivity and a corneal reflex. With decreasing barbiturate blood levels, Pa component latency remained constant (30 to 31 ms), while amplitude systematically increased from less than 0.19 uv to 1.00 uv. There was no detectable crossed or uncrossed acoustic reflex activity until barbiturate blood levels were less than 15 μg/ml (refer again to Fig. 2). Consistently normal reflex threshold levels (85 to 95 dB HL) were only observed following total clearance of detectable barbiturates in the blood. Throughout barbiturate coma, tympanograms were type A (22) and static compliance values were normal (0.30–0.35 cm^3) bilaterally. Statistical correlations among auditory and physiologic data are summarized in Table II.

Table I. *Chronological summary of physiologic, neurologic and auditory evoked response data for a 38-year-old male sustaining an acute, severe cerebrovascular insult (case 1)*

Data were initially obtained on the first day post insult. MAP = mean arterial pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure. + = normal; − = abnormal; 0 = no response; NA = data not available

	Time in hours re: tapering of barbiturates								
Parameter	−34	0	4	8	20	32	56	80	104
Physiologic									
Barbiturate blood level (μg/ml)	34	36	NA	31	NA	15	5.7	0.2	0
Body temperature (°F)	99	100	99	98.6	99	99.8	100	102	100
MAP, mmHg	84	92	95	96	94	99	100	97	93
ICP, mmHg	0	1	2	0	0	0	0	NA	NA
CPP, mmHg	84	91	93	96	94	99	100	NA	NA
PaO_2, mmHg	117	NA	NA	116	159	154	166	136	124
$PaCO_2$, mmHg	24	NA	NA	27	35	32	34	34	36
Neurologic									
Pupillary response (size, mm/reactivity)	3/0	3/0	4/0	3/0	4/−	3/+	5/+	4/+	4/+
Corneal reflex	0	0	0	0	−	−	−	+	+
Purposeful motor response to pain	0	0	0	0	0	0	0	−	+
Auditory evoked response									
Acoustic reflex	0	0	0	0	0	0	−	−	+
Brainstem (latency)	+	+	+	+	+	+	+	+	+
Middle-latency (amplitude)	0	0	0	0	−	−	−	+	+

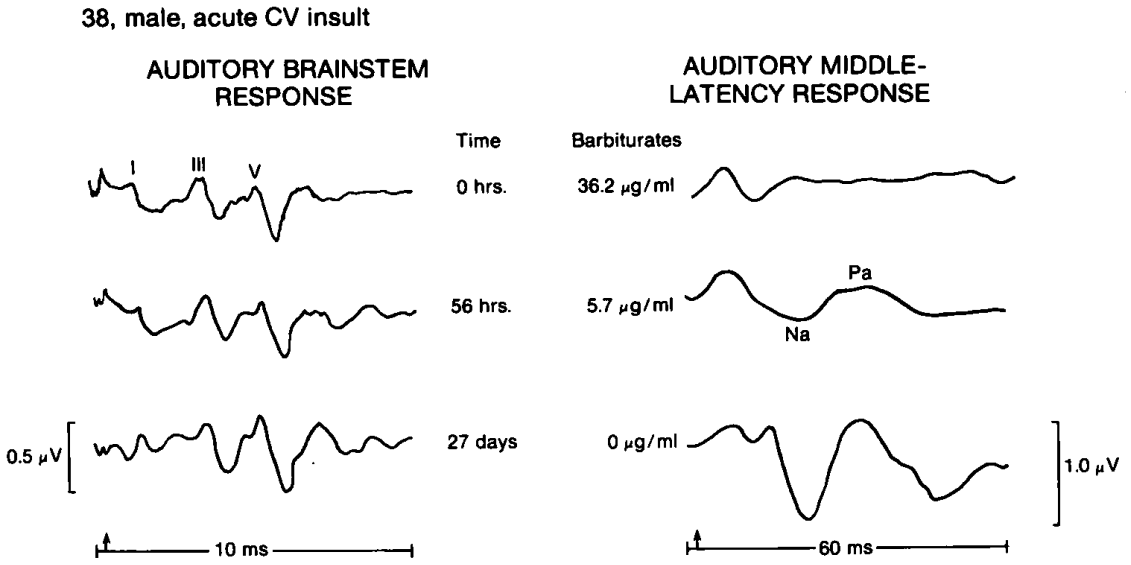

Fig. 1. Representative serial auditory brainstem and middle-latency response recordings for a 38-year-old male with acute, severe cerebrovascular insult during emergence from barbiturate coma (case 1). Time is relative to initial tapering of barbiturates.

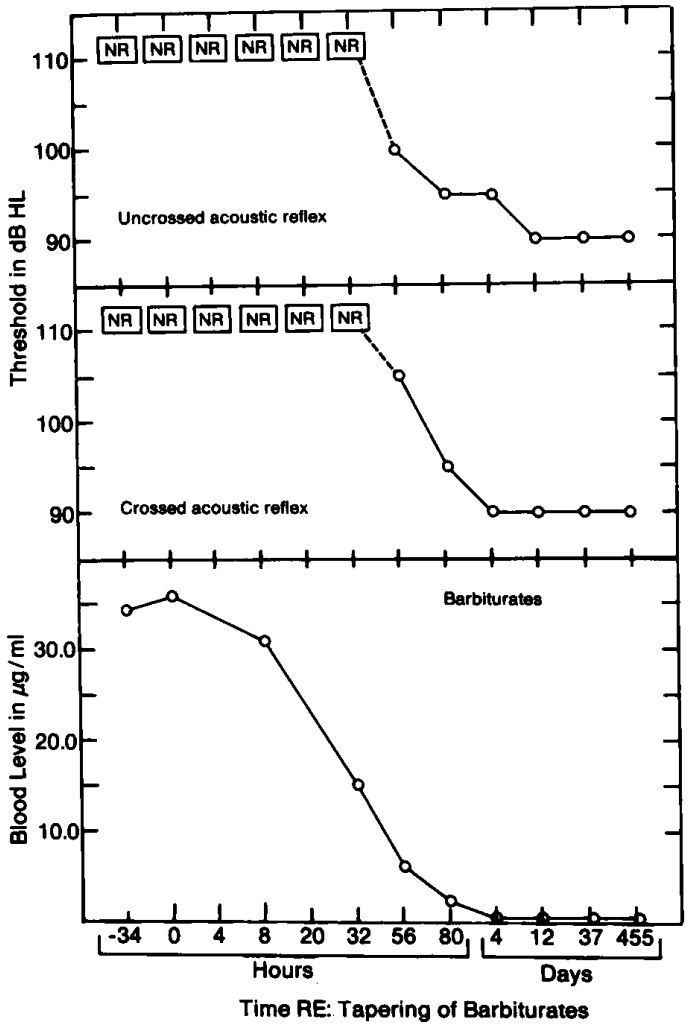

Fig. 2. Contralateral (crossed) and ipsilateral (uncrossed) acoustic reflex threshold levels for case 1 during emergence from barbiturate coma.

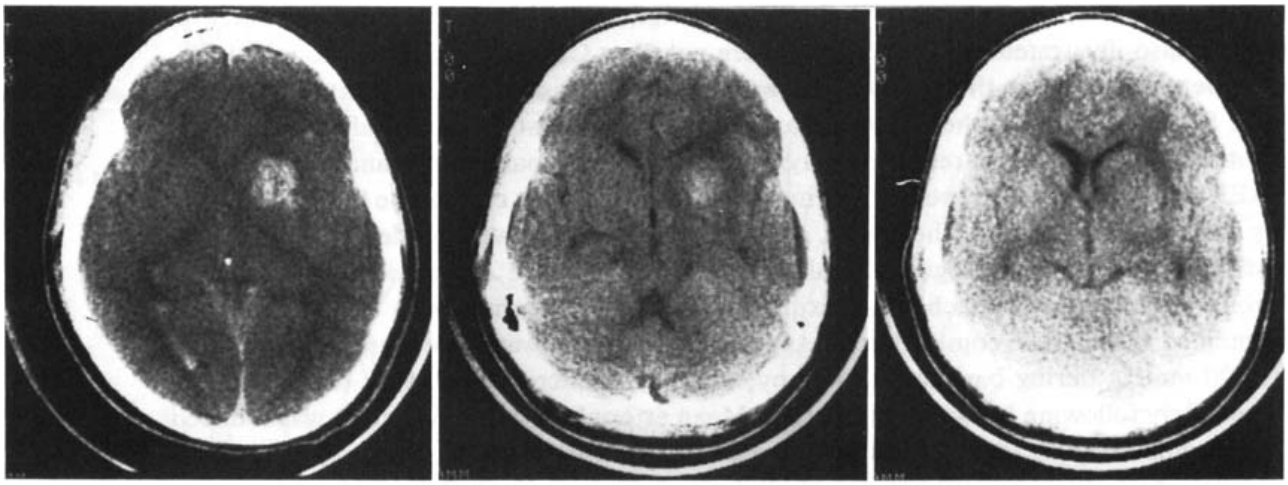

Fig. 3. Computerized tomography scans for a 17-year-old male with acute, severe closed head injury (case 2). On the day of injury (left) and second (middle) and 15th (right) post injury days.

Case 2

A 17-year-old male was involved in a motor vehicle accident. He was the driver and was thrown from the vehicle. There was immediate loss of consciousness. At the scene, a Glascow Coma Score of 6 indicated a severe head injury. Pupils were pinpoint and nonreactive bilaterally. There was a deviate gaze to the right. Spontaneous decerebration was noted. A corneal reflex was present, but there was no gag reflex and no apparent spontaneous respiration. The patient was transported via helicopter to the Hermann Hospital. He was treated with steroids (Decadron) and Mannitol in route. CT on admission revealed multiple scattered hemorrhagic contusions, diffuse cerebral edema and intraventricular hemorrhage (see Fig. 3). Follow-up CT scans on post injury days 2, and 15,

Table II. *Summary of correlations among auditory and physiologic parameters for cases 1 and 2*

MAP = mean arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure; PaO_2 = arterial pressure of oxygen; $PaCO_2$ = arterial pressure of carbon dioxide. + = correlation significant at $p<0.01$ level of confidence; − = correlation not significant at $p<0.01$ level of confidence

	Physiologic parameters for cases 1 and 2													
	Barbiturate		Temperature		MAP		ICP		CPP		PaO_2		$PaCO_2$	
Auditory parameter	1	2	1	2	1	2	1	2	1	2	1	2	1	2
Brainstem response														
Latency I–III	−	−	−	−	−	−	−	−	−	−	−	+	−	+
Latency III–V	−	−	+	−	−	−	−	−	−	−	−	−	−	−
Latency I–V	−	−	+	−	−	−	−	−	−	−	−	−	−	−
Amplitude I	−	−	−	+	−	−	−	−	−	−	−	−	−	−
Amplitude III	+	−	−	−	−	−	−	−	+	−	−	−	+	−
Amplitude V	+	−	+	−	−	−	−	−	−	−	−	−	−	−
Middle-latency response														
Latency Na	−	−	−	+	−	−	−	−	−	−	−	−	−	−
Latency Pa	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Amplitude Na–Pa	+	−	+	−	−	−	−	−	−	−	−	−	−	−

showed reduced edema, and the development of bilateral subdural hygromas and cerebral atrophy, also illustrated in Fig. 3. There were no other CT changes. After the initial CT, the patient was taken to the operating room for a ventriculostomy (ICP monitor) and then to the SICU. Barbiturate therapy was started on the third post injury day after repeatedly elevated ICP that failed to respond to hyperventilation and maximum Mannitol therapy.

AER data were collected before, during and after barbiturate coma. The first assessment was done within 6 hours of the injury, and repeated measures were made through 22 days post injury. Serial physiologic, neurologic and AER data are summarized in Table III. Barbiturate blood level reached a maximum of 66 μg/ml. Normal body temperature was maintained throughout coma. Blood oxygen values were always adequate. ICP was less than 20 mmHg during barbiturate therapy, although it increased slightly (to 21 mmHg) immediately following barbiturate tapering. Mean arterial pressure, however, was reduced during coma resulting in a substantial decrease in cerebral perfusion pressure. Neurologic responsiveness was decreased in deep barbiturate coma.

As illustrated in Fig. 4, a well-formed ABR was reliably recorded before, during and after barbiturate therapy. Absolute and interwave (I–III and III–V) latency values were consistently within normal limits. Amplitude was never abnormally reduced. On post injury days 4 through 12, amplitude of the wave I component (0.65 uv) exceeded the upper limits of our normative data. The AMR was initially poorly-formed and of small amplitude, as shown in Fig. 5, with a bi-peaked Pa complex. By post injury day two, however, there was a reliable and well-formed AMR. During barbiturate therapy, the AMR Pa component was not observed. A positive-voltage deflection immediately following the Na wave appeared to be related to filter artifact. It was not recorded with a wider filter bandpass setting (5 to 1500 Hz vs. 30 to 100 Hz). On the first test day that barbiturates were not

Table III. *Chronologic summary of physiologic, neurologic and auditory evoked response data for a 17-year-old male with severe closed head injury (case 2)*

Data were initially obtained within 6 hours post injury. MAP = mean arterial pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure + = normal; − = abnormal; 0 = no response; NA = data not available

	Post injury day										
Parameter	0	1	2	4	5	9	11	12	15	17	22
Physiologic											
Barbiturate blood level (μg/ml)	0	0	0	39	66	15	3	0	0	0	0
Body temperature (°F)	99	100	100	100	102.6	101	102	99	99	101	99
MAP, mmHg	113	117	113	87	90	70	97	110	77	107	127
ICP, mmHg	7	22	15	18	17	16	18	21	14	NA	NA
CPP, mmHg	106	95	98	69	73	54	79	89	63	NA	NA
PaO_2, mmHg	185	147	121	139	133	NA	122	143	163	205	112
$PaCO_2$, mmHg	32	30	30	35	26	NA	32	30	39	43	44
Neurologic											
Pupillary response (size/reactivity)	2/−	2/+	1/−	2/0	2/0	3/0	2/+	3/+	4/+	4/+	2/+
Best motor response strength	−	−	−	0	0	0	0	0	−	−	−
Auditory evoked response											
Brainstem (latency)	+	+	+	+	+	+	+	+	+	+	+
Middle-latency (amplitude)	−	+	+	0	0	0	0	−	−	0	+

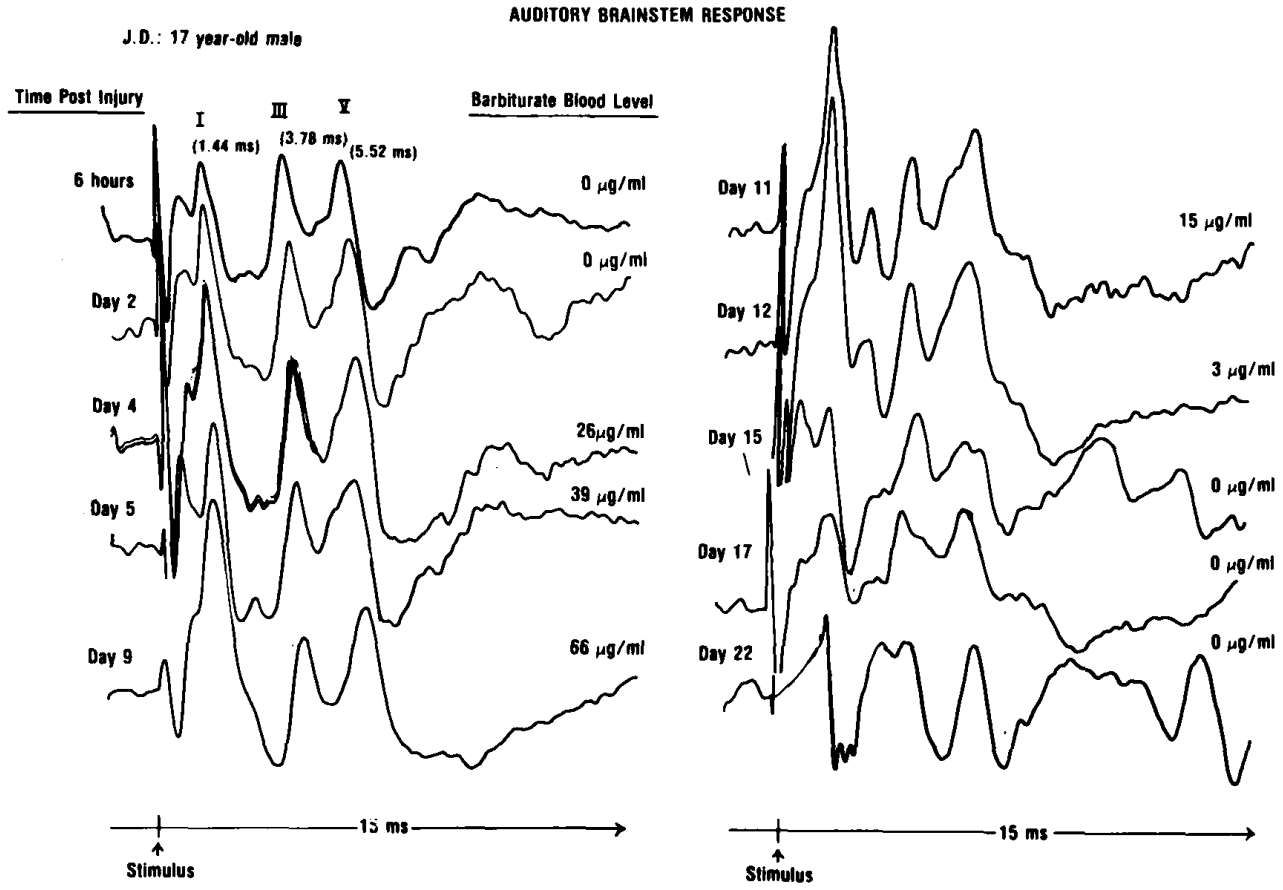

Fig. 4. Serial auditory brainstem response recordings before, during and after barbiturate coma for case 2. (Reprinted with permission from Jacobson, JT. The Auditory Brainstem Response. San Diego, CA: College-Hill Press, 1985.)

detected by blood analysis, we consistently measured in a Pa component of abnormally large amplitude (greater than 2 uv). Latency was consistent with pre-barbiturate values (24 msec). The patient was chemically paralyzed at the time of testing. After barbiturate coma a normal-appearing AMR was not recorded until the 22nd post injury day. Statistical correlations among auditory and physiologic data are summarized in Table II.

DISCUSSION

High-dose barbiturates differentially influence the acoustic reflex, and the auditory brainstem and middle-latency responses. Consistent with previous experimental investigations, we found clinically that ABR latency is resistant to the effect of barbiturates. The data reported in this paper typify our clinical experiences. We have analyzed serial ABR findings for over 25 severely head-injured patients in therapeutic barbiturate-induced coma. A reliable, well-formed and clinically normal ABR has been repeatedly recorded from patients with barbiturate blood levels in excess of 100 μg/ml, and with drug-suppressed neurologic signs. In contrast, the AMR and acoustic reflex are invariably not observed in deep barbiturate coma, and are usually first recorded coincident with reappearance of clinical neurologic signs of brainstem functioning. Unexpectedly, an unusually large-amplitude AMR Pa component is sometimes recorded with the initial release from barbiturates, as illustrated in case 2.

The two patients reported in this paper sustained an acute, severe brain injury. Although neurologic and physiologic parameters were carefully documented in each case, we were

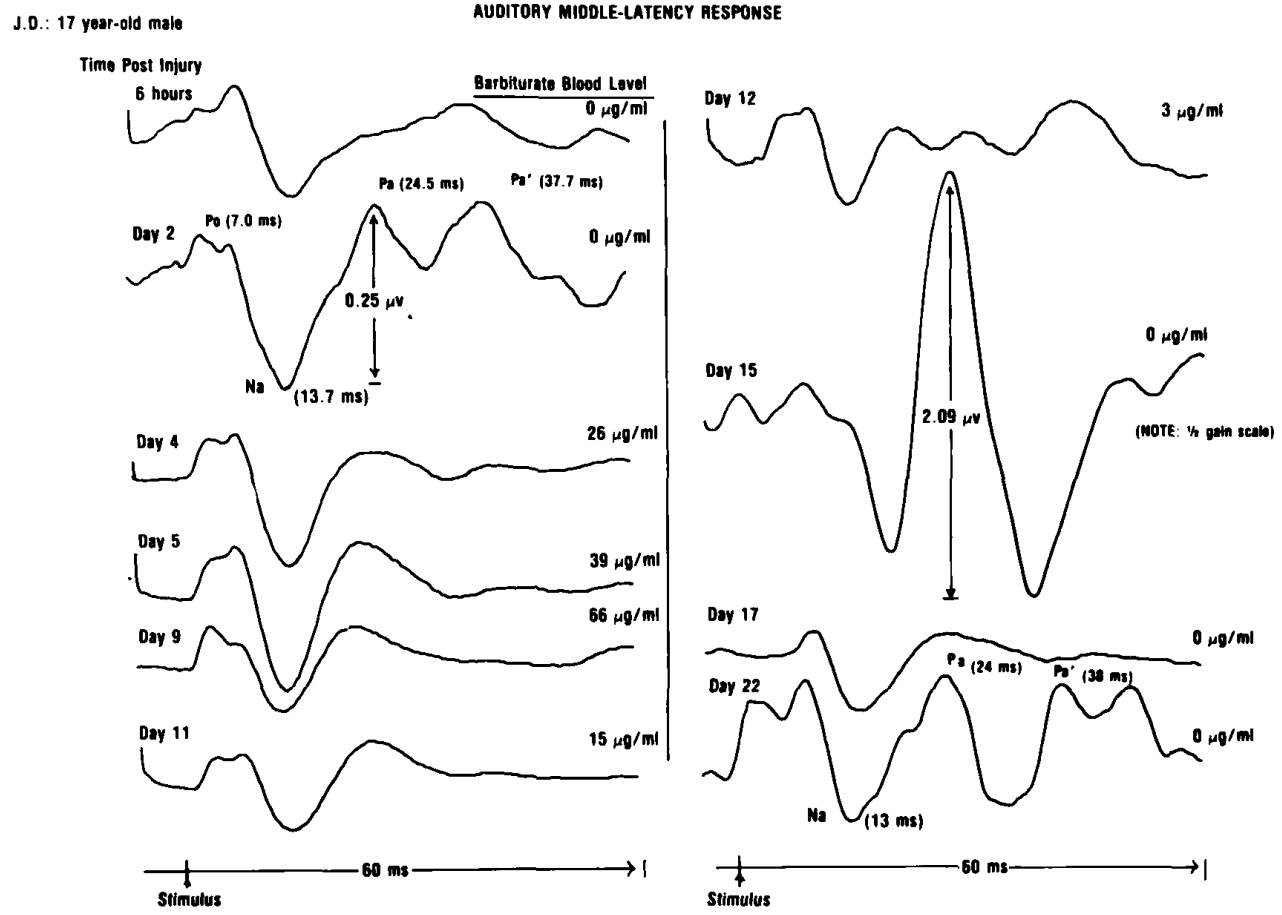

Fig. 5. Serial auditory middle-latency response recordings before, during and after barbiturate coma for case 2.

unable to rule out the possibility that dynamic brain pathophysiology influenced auditory response outcome. In case 1, important parameters, such as body temperature, ICP and blood gases, were stable throughout the study. There was an appropriate temporal correspondence among re-appearance of the acoustic reflex, AMR, pupillary response and the corneal reflex. In case 2, body temperature, ICP and CT findings were reasonably constant and blood gases were adequate, but decreased mean arterial pressure in deep barbiturate coma resulted in reduced cerebral perfusion pressure. It is possible that cerebral perfusion was a factor in the AMR changes. However, suppression of the AMR was noted coincident with absence of pupillary response, and in the presence of a reliably-recorded ABR. Furthermore, on the 15th post injury day (see Table II), there were no barbiturates in the blood, and an AMR was observed with very low cerebral perfusion pressure (63 mmHg). In any event, this pattern of findings illustrates the importance of considering numerous variables in the study of auditory responses and barbiturates.

Statistical correlation of barbiturate blood levels, physiologic parameters and auditory findings was completed, but did not confirm nor clarify the above-noted relationships among these factors (refer to Table II). In studying clinically the influence of barbiturates on auditory measures, it is not possible to adhere to the cardinal rule of experimental single case research, that is, manipulation of only one variable at a time (23). Nor is it clinically feasible to introduce, withdraw and reintroduce the variable of interest (barbiturates). The appropriateness of clinical vs. statistical criteria for significance of changes in serial data is open to question (24). Indeed, the use of statistical analysis of single case clinical data, in general, is controversial (25). We elected, therefore, to evaluate the

importance of changes in serial auditory findings for the two cases in the context of clinical normative data. Experimental and normative data were obtained by the same tester with the same instrumentation.

The neurophysiologic bases for the different effects of barbiturates on these three auditory nervous system responses are not known. In classic studies more than 30 years ago, Magoun, Moruzzi, French and colleagues provided experimental evidence that auditory stimulation may generate neural impulses that are conducted simultaneously toward the cortex via two sets of pathways (26–28). One system was direct, characterized by "spike-like" potentials with brief latencies recorded in the lateral sensory pathways, and not influenced by anesthesia. The other system was diffuse, characterized by potentials with more sloping, "wave-like" morphology and distinctly larger latency, recorded in the medial brainstem, and suppressed by barbiturate anesthesia. Subsequent experiments by these investigators, and numerous other eminent auditory neurophysiologists, confirmed the suppression of middle-latency auditory responses (4–8, 29–35) and the acoustic reflex (2) by high-dose barbiturates, and implicated the role of the reticular formation.

The profound influence of barbiturates on the acoustic reflex and AMR, yet not the ABR, is probably related to the neurophysiologic substrate of these responses. There is general agreement that the acoustic reflex and middle-latency response have multi-synaptic pathways, characteristic of CNS events mediated by the reticular formation (2, 28, 29, 36). The AMR is probably cortically-generated (37–39) and the acoustic reflex may also be cortically influenced (1). Even the rostral most component of the ABR (wave V), on the other hand, may reflect activity of only third or fourth order neurons and, therefore, may be dependent on activity of only two or three synapses in the brainstem (40). Multiple bases for the alteration of synaptic activity by barbiturates have been suggested, including reduction of pre-synaptic neurotransmitter release, increased postsynaptic chloride ion conduction and augmentation of post-synaptic amino acid-mediated inhibition (41–44). The differential influence of barbiturates on the three auditory responses may be the result of a complex interaction among these synaptic mechanisms, the number of synapses involved in the response and differences in the functional types of neurons subserving the response.

The present study yielded two findings that were not anticipated, and deserve special mention. First, although ABR latency was not markedly altered in barbiturate coma, there was clinically significant amplitude augmentation of the wave I component in case 2. We have since recorded an abnormally large wave I component in other patients during deep barbiturate coma, and have also observed the phenomenon in patients with gross brainstem and cerebral dysfunction (45, 46). Visual inspection of the serial ABR waveforms displayed by Marsh and colleagues (12, 13) revealed an apparent increase in wave I amplitude with high-dose barbiturates administration in cats, although the authors did not make note of this finding. We can only speculate as to possible explanations. As illustrated in case 1, the acoustic reflex is suppressed by barbiturates. The augmentation of wave I amplitude may reflect cochlear function without the sound-attenuating influence of the stapedius muscle. Holstein et al. (30) found experimental evidence of increased cochlear nucleus multiple unit activity with middle ear muscle paralysis. There are three factors, however, arguing against this possibility: 1) The ABR occurs within 5 to 6 msec after the stimulus, whereas the latency of stapedius muscle contraction in the acoustic reflex is at least 10 msec (47); 2) acoustic reflex sound-attenuation is mainly for frequencies below 1000 Hz (48) and the ABR is dependent on cochlear activity in the frequency region above 1000 Hz (49); and 3) we have not consistently observed changes in ABR wave I in non-barbiturate treated patients who are chemically paralyzed. Therefore, rather than middle ear muscle paralysis, we suggest that the barbiturates exert a direct influence on inhibition and excitation processes in the auditory nervous system (31). That is, the function of

certain decending efferent and presumably inhibitory auditory centers, particularly olivocochlear pathways, may be suppressed (50–52). Whatever the mechanism, wave I amplitude augmentation is the most pronounced effect of high-dose barbiturates on the ABR, and must be taken into account in the clinical interpretation of relative amplitude measures (e.g. wave V/I amplitude ratio) in comatose patients.

A second unexpected finding was the sequence of AMR changes during recovery from barbiturate coma. For case 2 the AMR Pa component was excessively large (2 uv) bilaterally on the first post-coma test day that no barbiturate blood level was detected. Then, there was no observable AMR for approximately four days. We are uncertain as to whether the augmented AMR and subsequent apparent suppression is a direct effect of barbiturates, perhaps reflecting a synaptic hyperactivity followed by reduced activity, or a component of a generalized CNS process, such as post-barbiturate seizure activity, or even another neurophysiologic aberration. We consider post-auricular muscle (PAM) artifact an unlikely explanation since the patient was chemically paralyzed at the time of testing, and the latency of the AMR wave was consistent with our normative data for Pa, and well outside of the latency region of the PAM (10 to 15 msec) reported by others (53). The post-barbiturate AMR pattern brings to mind observations made by Pradhan & Galambos (4) over 20 years ago following a comprehensive experimental investigation with cats. Namely, changes in AER's during recovery from barbiturate anesthesia are not necessarily the reverse of events observed during entry into anesthesia. Also, with release from barbiturates, portions of the cortical AER's may be enhanced. And, finally, even after a subject (cat) appears to be behaviorally intact, the AER's may not yet be comparable to pre-anesthetic recordings.

In conclusion, the results of the present study have implications for basic investigations and clinical applications of the acoustic reflexes and auditory evoked responses. The validity of acoustic reflex, AMR, and perhaps 40 Hz response (46) data obtained from animal models is compromised by the use of barbiturate anesthesia. Generalization of experimental AER findings to man is, therefore, dubious unless measurement conditions and subject state are equivalent (54). Clinically, the ABR appears to have value in monitoring CNS status of acute brain-injured patients in therapeutic barbiturate coma (45, 46), when traditional neurologic signs are suppressed. The acoustic reflex and AMR, on the other hand, are of little value in barbiturate coma, yet may offer an electrophysiologic measure of earlier effects of anesthetics on the CNS. Further study of the interactions among barbiturates and these other auditory measures is likely to provide both basic and clinical information on auditory neurophysiology.

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REFERENCES

1. Baust W, Berlucci G. Reflex response to clicks of cat's tensor tympani during sleep and wakefulness and the influence thereon of the auditory cortex. Arch Ital Biol 1964; 102: 686–712.

2. Borg E, Moeller AR. Effect of central depressants on the acoustic middle ear reflex in rabbit. Acta Physiol Scand 1975; 94: 327–88.
3. Carmel P, Starr A. Acoustic and nonacoustic factors modifying middle ear muscle activity in waking cats. J Neurophysiol 1963; 26: 598–616.
4. Pradhan SN, Galambos R. Some effects of anesthetics on the evoked responses in the auditory cortex of cats. J Pharmacol Exp Ther 1963; 139: 97–106.
5. Goff WR, Allison T, Lyons W, Fisher TC, Conte R. Origins of short latency auditory evoked potentials in man. Prog Clin Neurophysiol 1977; 2: 30–44.
6. Harada K, Ichikawa G, Koh M, Uchiclida T. Effects of anesthesia on the middle latency components in cat. Audiol Jap 1980; 23: 150–8.
7. Buchwald JS, Weber DS, Holstein SB, Grover FS, Schwafel JA. Quantified unit background activity in the waking cat during paralysis, anesthesia and cochlear destruction. Brain Res 1969; 15: 465–82.
8. Buchwald JS, Hinman C, Norman RJ, Huang CM, Brown KA. Middle- and long-latency auditory evoked response recorded from the vertex of normal and chronically lesioned cats. Brain Res 1981; 205: 91–109.
9. Bobbin RP, May JG, Lemoine RL. Effects of pentobarbital and ketamine on brainstem auditory potentials. Arch Otolaryngol 1979; 105: 467–70.
10. Cohen M, Britt, R. Effects of anesthetics on the brainstem evoked response. Soc Neurosci Abstr 1981; 7: 282.
11. Kaga K, Takahashi K, Suzuki I. Effects of pentobarbital and ketamine intoxication on auditory brain stem evoked responses in cat. Electroencephalogr Clin Neurophysiol 1977; 43: 895.
12. Marsh RR, Frewen TC, Sutton LN, Potsic WP. Resistance of the auditory brainstem response to high barbiturate levels. Otolaryngol Head Neck Surg 1984; 92: 685–688.
13. Sutton LN, Frewen T, Marsh R, Jaggi J, Bruce D. The effects of deep barbiturate coma on multimodality evoked potentials. J Neurosurg 1982; 57: 178–85.
14. Goth A. Medical pharmacology. Principles and concepts. 7th ed. St. Louis: C.V. Mosby, 1974.
15. Bosatra A, Russolo M, Poli P. Modifications of the stapedius muscle reflex under spontaneous and experimental brain-stem impairment. Acta Otolaryngol 1975; 80: 61–6.
16. Borg E, Moeller AR. Effect of ethylalcohol and pentobarbital sodium on the acoustic middle ear reflex in man. Acta Otolaryngol (Stockh) 1967; 64: 415–26.
17. Robinette MS, Rhoads EP, Marion MW. Effects of secobarbital on impedance audiometry. Arch Otolaryngol 1974; 100: 351–3.
18. Starr A, Achor J. Auditory brainstem responses in neurological disease. Arch Neurol 1975; 32: 761–8.
19. Newlon PG, Greenberg RP, Enas GG, Becker DP. Effects of therapeutic pentobarbital coma on multimodality evoked potentials recorded from severely head-injured patients. Neurosurgery 1983; 12: 613–9.
20. Rossi GT, Britt RH. Effects of hypothermia on the cat brain-stem auditory evoked response. Electroencephalogr Clin Neurophysiol 1984; 57: 143–55.
21. Marshall NK, Donchin E. Circadian variation in the latency of brainstem response and its relation to body temperature. Science 1981; 212: 356–8.
22. Hall JW III, Jerger JF. Impedance audiometry. In: Lass NJ, McReynolds LV, Northern JL, Yoder DE, eds. Speech, language, and hearing. Vol. III. Hearing disorders. Philadelphia: WB Saunders, 1982: 968–81.
23. Hersen M, Barlow DH. Single-case experimental designs: strategies for studying behavior change. New York: Pergamon Press, 1976.
24. Kazdin AE. Statistical analyses for single-case experimental designs. In: Hersen M, Barlow DH, eds. Single case experimental designs. New York: Pergamon Press, 1976: 265–316.
25. Michael J. Statistical inference for individual organism research: mixed blessing or curse? J Applied Behav Anal 1974; 7: 647–53.
26. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1949; 1: 455–73.
27. French JD, Amerongen FK, Magoun HW. An activating system in the brain stem of monkey. Arch Neurol Psychiatry (Chicago) 1952; 68: 577–90.
28. French JD, Verzeano M, Magoun HW. An extra-lemniscal sensory system in the brain. Arch Neurol Psychiatry 1953; 69: 505–18.
29. Arduini A, Arduini MG. Effect of drugs and metabolic alterations on brain stem arousal mechanism. J Pharmacol Exp Therap 1954; 110: 76–85.
30. Holstein SB, Buchwald JS, Schwafel JA. Tone response patterns of the auditory nuclei during normal wakefulness, paralysis and anesthesia. Brain Res 1969; 15: 483–99.

31. Dafny N. Neurophysiological approach as a tool to study the effects of drugs on the central nervous system: Dose effect of pentobarbital. Exp Neurol 1978; 59: 263–74.
32. Nakai Y, Shimamoto K, Takaori S, Matsuoka I. Influence of central depressants on the central auditory response in the cat. Int Audiol 1966; 5: 176–9.
33. Nakai Y, Takaori S, Shimamoto K. Effects of central depressants on the evoked potentials in the inferior colliculus caused by acoustic stimuli in the cat. Jap J Pharmacol 1965; 15: 201–9.
34. Hungerbruhler JP, Saunders JC, Greenberg J, Reivich M. Functional neuroanatomy of the auditory cortex studies with (2-^{14}C) deoxyglucose. Exp Neurol 1981; 71: 104–21.
35. Kiang NY, Neame JH, Clark LF. Evoked cortical activity from auditory cortex in anesthetized and unanesthetized cats. Science 1961; 133: 1927–8.
36. Brodal A. Neurological anatomy in relation to clinical medicine. 3rd ed. New York: Oxford University Press, 1981: 497–8, 632.
37. Celesia GG. Organization of auditory cortical areas in man. Brain 1976; 15: 465–82.
38. Kaga K, Hink RF, Shinoda Y, Suzuki J. Evidence for a primary cortical origin of a middle latency auditory evoked potential in cats. Electroencephalogr Clin Neurophysiol 1980; 50: 254–66.
39. Lee YS, Lueder H, Dinner DS, Lesser RO, Hahn J, Klem G. Recording of auditory evoked potentials in man using chronic subdural electrodes. Brain 1984; 107: 115–31.
40. Tsuchitani C. Physiology of the auditory system. In: Moore EJ, ed. Bases of auditory brain-stem evoked responses. New York: Grune and Stratton, 1983: 67–108.
41. MacDonald RL, Barker JL. Anticonvulsant and anesthetic barbiturates: Different postsynaptic actions in cultured mammalian neurons. Neurology 1979; 29: 432–47.
42. Heyer EJ, MacDonald RL. Barbiturate reduction of calcium dependent action potentials: Correlation with anesthetic action. Brain Res 1982; 236: 157–71.
43. Sivam SP, Nabeshima T, Ho IK. Acute and chronic effects of pentobarbital in relation to postsynaptic GABA receptors: A study with muscimal. J Neurosci Res 1982; 7: 37–47.
44. Schultz D, MacDonald RL. Barbiturate enhancement of GABA-mediated inhibition and activation of chloride ion conductance: Correlation with anticonvulsant and anesthetic actions. Brain Res 1981; 209: 177–88.
45. Hall JW III, Mackey-Hargadine J. Auditory evoked responses in severe head injury. Seminars in Hearing 1984; 5: 313–336.
46. Hall JW III, Mackey-Hargadine J, Allen SJ. Monitoring neurologic status of comatose patients in the intensive care unit. In: Jacobson JJ, ed. Auditory brainstem response audiometry. San Diego: College-Hill Press, 1985: 253–283.
47. Moeller AR. Intra-aural muscle contraction in man examined by measuring acoustic impedance of the ear. Laryngoscope 1958; 68: 48–62.
48. Moeller AR. Network model of the middle ear. J Acoust Soc Am 1961; 33: 168–76.
49. Coats AC, Martin JL. Human auditory nerve action potentials and brainstem evoked responses. Effect of audiogram shape and lesion location. Arch Otolaryngol 1977; 103: 605–22.
50. Warr WB. The olivocochlear bundle: its origins and terminations in the cat. In: Norton RF, Fernandez C, eds. Evoked electrical activity in the auditory nervous system. New York: Academic Press, 1978: 43–65.
51. Rasmussen G. Efferent fibers of the cochlear nerve and cochlear nucleus. In: Rasmussen GL, Windle W, eds. Neural mechanisms of the auditory and vestibular systems. Springfield, Ill: CC Thomas, 1960: 105–15.
52. Gacek RR. Efferent innervation of the labyrinth. Am J Otolaryngol 1984; 5: 204–24.
53. Kileny P. Auditory evoked middle-latency responses: current issues. Seminars in Hearing 1983; 4: 403–13.
54. Merzenich MM, Gardi JN, Vivion MC. Animals. In: Moore EJ, ed. Bases of auditory brain-stem evoked responses. New York: Grune and Stratton, 1983: 391–412.