

Scopolamine, Morphine, and Brain-stem Auditory Evoked Potentials in Awake Monkeys

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The effects of scopolamine and morphine sulfate on brain-stem auditory evoked potentials (BAEPs) were studied in 10 rhesus (*Macaca mulatta*) monkeys. Study drugs were given intravenously to unanesthetized animals and BAEPs recorded at 3-min and 30-min intervals after administration of 0.1 mg/kg and 0.32 mg/kg of scopolamine and 15 min after administration of 3.2 mg/kg morphine at the end of the experiment. No significant change in either latency or amplitude of different components of BAEPs was observed. (Key words: Analgesics: morphine. Brain: evoked potentials, auditory. Parasympathetic nervous system: scopolamine. Premedication: morphine; scopolamine.)

IN THE LAST DECADE, developments in computer technology have led to increasing utilization of brain-stem auditory evoked potentials (BAEPs) in clinical practice. Various clinical applications of BAEPs have been defined,¹ and brain-stem electric response audiometry (BERA) has become a useful tool in the armamentarium of otologists.² On many occasions, BERA is done under general anesthesia either because the patient is too young, uncooperative, mentally retarded, or is being anesthetized for another surgical procedure, and BERA is combined at the same time. Previously published reports have shown that, while BAEPs are preserved under general anesthesia,³ different anesthetics have different effects on the latencies of various components of BAEP. No significant change was seen with halothane,⁴ pentothal,⁴ and fentanyl,⁵ while enflurane⁶ and isoflurane⁷ anesthesia have been shown to cause significant prolongations of both absolute and interpeak latencies of BAEPs. Therefore, it is important that anesthesiologists involved in taking care of patients undergoing BERA be familiar with the effects on BAEPs of all drugs used during anesthesia, including those used for premedication. In a previous study⁵ we observed a prolongation of the absolute latency of the early waves of BAEPs in patients premedicated with scopolamine hy-

drobromide and morphine sulfate, which, however, was not statistically significant. A prolongation of the absolute latency of wave I and its following components, with normal interpeak latencies, can be interpreted as being indicative of a conductive hearing loss. Cholinergic mechanisms have been shown to be involved in the generation of auditory evoked response in rats.⁸ Clinical usefulness of scopolamine in motion sickness⁹ suggests a possible effect on the eighth nerve and its synapses in medullary centers. It therefore is conceivable that use of scopolamine for premedication in our previous study might have resulted in the prolongation of latencies of the BAEPs.⁵ On the other hand, technical factors like change in stimulus strength contributing to prolonged latencies could not be ruled out because BAEPs before and after premedication were recorded in two different environments with different background noise levels. We therefore designed this study to evaluate the effects of scopolamine and morphine on BAEPs in monkeys. An animal (*Macaca mulatta*) model was chosen for ease of establishing a dose response curve should the drug used show an alteration of BAEPs. The choice of a rhesus monkey as an animal model was based on its closeness to humans on the phylogenetic scale and because normative data on BAEPs in this species have been published previously.¹⁰

Materials and Methods

A total of 10 rhesus (*Macaca mulatta*) monkeys, of either sex (five male, five female), weighing 4.5–9.0 kg were studied in which BAEPs and the electroencephalogram (EEG) were recorded simultaneously. The monkeys were placed in a restraining chair in sitting position, and a peripheral vein was cannulated for administration of the drugs. Arterial blood pressure and heart rate were electronically measured and recorded once every 3 min using the Dinamap® vital signs monitor (Critikon, Tampa, Florida). Rectal temperature was monitored continuously using a digital thermometer (R.D.F. Corporation, Hudson, New Hampshire).

Stimulation and recording parameters used for recording the BAEPs are shown in table 1. Three subdermal needle electrodes were used; their location was Cz (midline central vertex) and the two mastoid processes.

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Therefore, a vertex to ipsilateral mastoid configuration was used, with the opposite mastoid acting as ground. BAEPs were recorded with a Nicolet CA-1000 Clinical Evoked Potentials Averager® (Nicolet Instrument Corp., Madison, Wisconsin). A Grass Model RPS-7C® polygraph was used for recording the EEG. Three channels were used to record the EEG from the frontal, parietal, and occipital areas using bipolar recordings.

In each monkey, three individual BAEP waveforms were recorded as control tracings to document reproducibility. To verify that the evoked response was truly stimulus related and not systematic artifact, the earphone was detached while the computer sampling still synchronized with auditory stimulus, and absence of various components of the BAEP was documented prior to proceeding with administration of drugs.

After recording control tracings of the BAEPs and the EEG, 0.1 mg/kg of scopolamine was given as a slow iv injection (over a period of 1 min) and recordings repeated at 3- and 30-min intervals after this injection. A second injection of 0.22 mg/kg of scopolamine then was given to achieve a cumulative dose of 0.32 mg/kg of scopolamine in each monkey and the BAEPs and the EEG recorded at intervals of 3 and 30 min. Finally, morphine 3.2 mg/kg was injected intravenously and tracings of the BAEPs and the EEG obtained 15 min later. A total of 60 observations were made. All waveforms were recorded in duplicate to document reproducibility.

All BAEPs waveforms were stored on floppy discs for subsequent measurement of absolute latencies and amplitudes of waves I, II, III, IV, and V and interpeak latencies of waves I through V.

TABLE 1. Stimulation and Recording Parameters Used for Recording the BAEPs

| |
|--|
| Site: Unilateral (right or left) insert ear phone, placed in the external auditory canal and taped in place. |
| Clicks: Positive (rarefaction) clicks |
| Intensity: 75 dB SL |
| Rate: 21/s |
| Duration: 100 μ s |
| Masking: None to the contralateral ear |
| Electrode placement: Both mastoid processes (M1 and M2) and central vertex (Cz) |
| Electrode impedance: <3 k Ω |
| Filters: 150–3,000 Hz |
| Analysis time: 10.2 ms |
| Repetitions per average: 2,000 |

Numeric data obtained for absolute and interpeak latencies and amplitude of various waveforms were subjected to one-way repeated measures analysis of variance. A *P* value less than 0.05 was considered significant. Significance levels reported in this study are those for Hotelling's *T*-square test statistic.¹¹ As latency and amplitude of wave V of BAEP was not measurable in all observations, only values (mean \pm SD) obtained are shown for this wave because repeated measures analysis of variance is not applicable to data with missing values.

Results

Administration of scopolamine was followed by gross behavioral changes. The monkeys demonstrated alternative periods of agitation, restlessness, and sedation. Pupillary dilation was noted within 3 min of the first injection of scopolamine in all monkeys, with a further increase in size of pupils following the second injection.

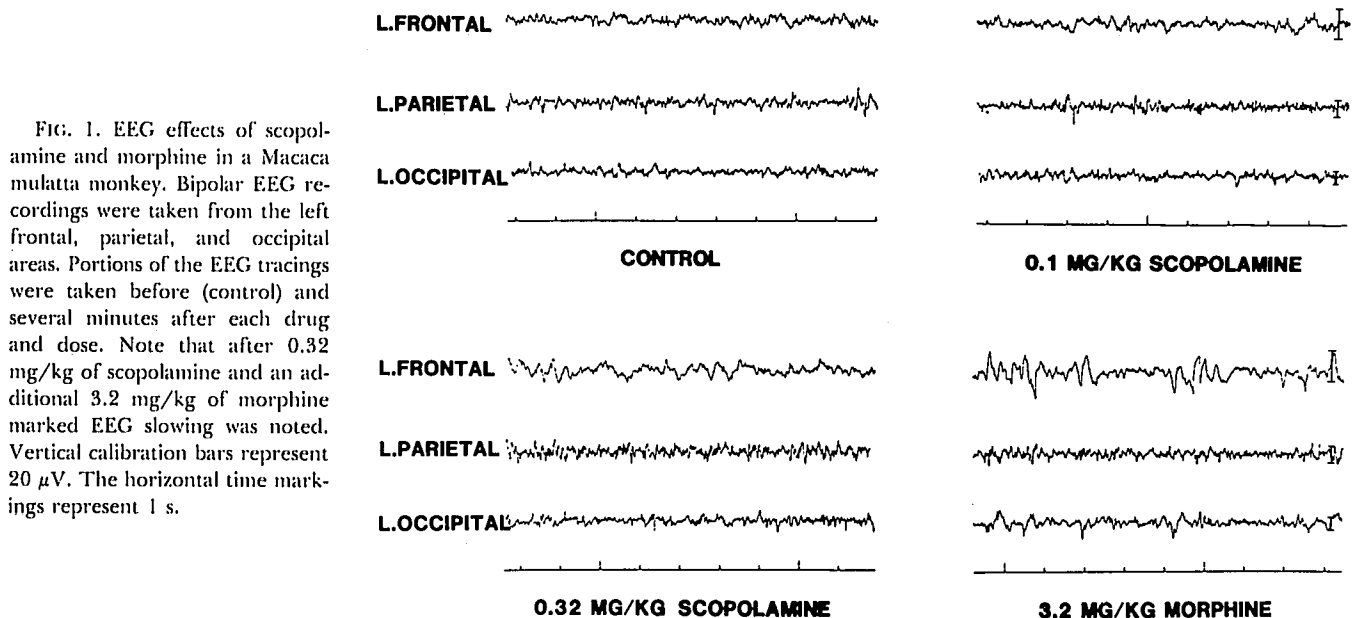


FIG. 1. EEG effects of scopolamine and morphine in a *Macaca mulatta* monkey. Bipolar EEG recordings were taken from the left frontal, parietal, and occipital areas. Portions of the EEG tracings were taken before (control) and several minutes after each drug and dose. Note that after 0.32 mg/kg of scopolamine and an additional 3.2 mg/kg of morphine marked EEG slowing was noted. Vertical calibration bars represent 20 μ V. The horizontal time markings represent 1 s.

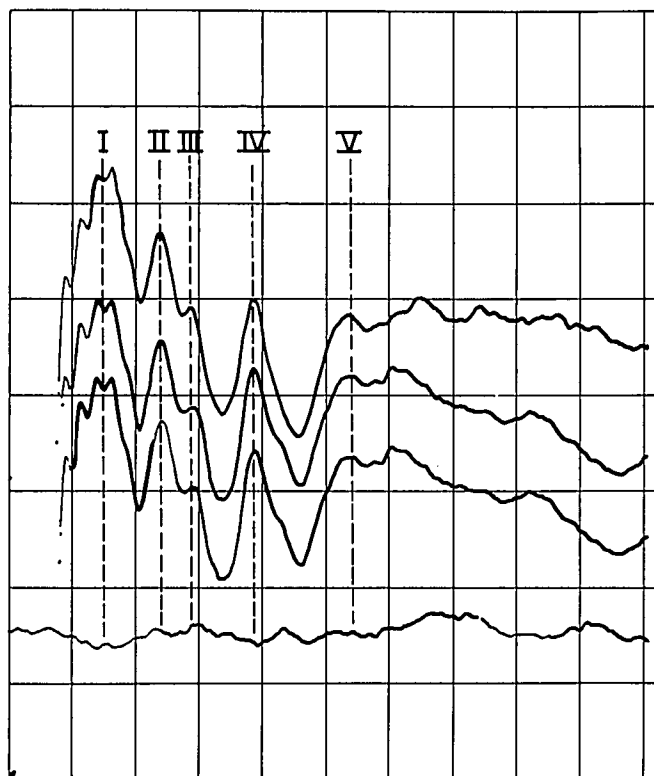


FIG. 2. Control tracings of the BAEPs in one monkey. Top three tracings demonstrate reproducibility in three separate averages of 2,000 stimuli each. Fourth tracing was recorded after disconnecting earphone while computer still was averaging same number of stimuli.

Wide fluctuations in heart rate and systemic arterial pressure were noted during the study period, depending upon whether the monkey was sedated or restless, but mean arterial pressure remained within 60–130 mmHg. Rectal temperature increased in every monkey following administration of scopolamine. The increase in temperature ranged from 0.5° C to 1° C. Administration of morphine resulted in sedation in every monkey.

Figure 1 shows the effect of scopolamine and morphine on the EEG in one monkey. This is representative of the EEG changes seen in all of the monkeys. Following the administration of 0.1 mg/kg scopolamine, no dramatic changes were seen. Following 0.32 mg/kg of scopolamine, there was an increase in the amplitude and a decrease in frequency. Administration of a subsequent dose of morphine enhanced this effect.

Technically satisfactory tracings of BAEPs could be obtained in all monkeys studied. A typical short latency BAEP is shown in figure 2, and five easily identifiable waves are indicated with roman numerals. Of these, wave V was the most difficult component to identify. We could not define wave V in one of the 10 monkeys in the control tracings, and this wave was unidentifiable in 13 of the 60 observations. The amplitude of each wave was measured from the peak to the next trough.

Table 2 summarizes the values for absolute latencies of the different waves of the BAEPs before and after the administration of scopolamine and morphine, while changes in interpeak latencies and amplitude are shown in tables 3 and 4, respectively. No significant change either in absolute or interpeak latencies could be attributed to the administration of scopolamine up to 0.32 mg/kg or an added dose of 3.2 mg/kg of morphine. Similarly, the amplitude of the different waves remained unchanged. Figure 3 illustrates the lack of effect of administration of scopolamine and morphine on the shape and latencies of the BAEPs in one monkey, which is representative of the population studied.

Discussion

The shape and the latencies of the different components of BAEPs in control tracings obtained in our study are comparable to previously published normative data in monkeys,¹⁰ using a vertex to earlobe reference

TABLE 2. Absolute Latencies in Milliseconds (Mean ± SD)

| Event | Waves | | | | |
|-------------------------------------|-------------|-------------|-------------|-------------|-------------|
| | I | II | III | IV | V |
| Control tracings | 1.60 ± 0.12 | 2.46 ± 0.11 | 3.21 ± 0.22 | 4.14 ± 0.16 | 5.64 ± 0.25 |
| 3 Min after 0.1 mg/kg scopolamine | 1.60 ± 0.13 | 2.46 ± 0.11 | 3.21 ± 0.22 | 4.14 ± 0.14 | 5.63 ± 0.22 |
| 30 Min after 0.1 mg/kg scopolamine | 1.60 ± 0.12 | 2.46 ± 0.11 | 3.22 ± 0.23 | 4.15 ± 0.14 | 5.56 ± 0.23 |
| 3 Min after 0.32 mg/kg scopolamine | 1.59 ± 0.13 | 2.48 ± 0.12 | 3.21 ± 0.22 | 4.16 ± 0.17 | 5.56 ± 0.24 |
| 30 Min after 0.32 mg/kg scopolamine | 1.60 ± 0.11 | 2.49 ± 0.12 | 3.22 ± 0.23 | 4.12 ± 0.15 | 5.50 ± 0.21 |
| 15 Min after 3.2 mg/kg morphine | 1.58 ± 0.16 | 2.46 ± 0.14 | 3.19 ± 0.24 | 4.13 ± 0.20 | 5.60 ± 0.25 |
| P value | 0.8 | 0.5 | 0.6 | 0.7 | * |

* Not subjected to statistical analysis because wave V could not be identified in 13 out of 60 observations made.

TABLE 3. Interpeak Latencies in Milliseconds (Mean \pm SD)

| Event | Waves | | | | |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | I-II | II-III | III-IV | IV-V | I-IV |
| Control tracings | 0.87 \pm 0.07 | 0.74 \pm 0.13 | 0.93 \pm 0.14 | 1.54 \pm 0.18 | 2.54 \pm 0.17 |
| 3 Min after 0.1 mg/kg scopolamine | 0.86 \pm 0.07 | 0.75 \pm 0.14 | 0.93 \pm 0.16 | 1.48 \pm 0.20 | 2.55 \pm 0.18 |
| 30 Min after 0.1 mg/kg scopolamine | 0.87 \pm 0.08 | 0.76 \pm 0.14 | 0.93 \pm 0.16 | 1.42 \pm 0.19 | 2.55 \pm 0.17 |
| 3 Min after 0.32 mg/kg scopolamine | 0.89 \pm 0.08 | 0.73 \pm 0.13 | 0.95 \pm 0.17 | 1.41 \pm 0.23 | 2.58 \pm 0.19 |
| 30 Min after 0.32 mg/kg scopolamine | 0.89 \pm 0.07 | 0.73 \pm 0.14 | 0.93 \pm 0.16 | 1.43 \pm 0.16 | 2.55 \pm 0.16 |
| 15 Min after 3.2 mg/kg morphine | 0.86 \pm 0.06 | 0.72 \pm 0.13 | 0.94 \pm 0.17 | 1.43 \pm 0.24 | 2.54 \pm 0.17 |
| P value | 0.3 | 0.8 | 0.7 | * | 0.5 |

* No statistical analysis because this interval was not calculated in 13 observations out of a total of 60.

for recordings. The use of awake nonpremedicated monkeys for this experiment has given us the opportunity to study the effect of scopolamine alone for the first part of the experiment without any possibility of an interaction between the study drug (scopolamine) and other drugs used to anesthetize the animals. Admittedly, having the animals unanesthetized led to greater fluctuations in systemic arterial pressure and heart rate following administration of scopolamine because of resulting restlessness, but these fluctuations in blood pressure did not cause any significant change in the BAEPs. The doses of scopolamine and morphine chosen in this study are much larger than those used clinically but are based on published studies in this animal model with atropine¹² and morphine.¹³ Behavioral change and pupillary dilation were noted following the first injection of scopolamine and were exaggerated further after the second dose, indicating that the drug level was sufficient to produce central nervous system (CNS) effects. This contention was supported further by an increase in body

temperature and slowing of EEG activity. We wish to emphasize that continuous recording of the EEG was not possible due to increased muscle artifact when the monkeys were agitated, so the EEG was recorded intermittently, only when the monkeys were sedated.

Our data show that scopolamine, when given in sufficient quantity to produce clinical and cortical EEG effects on CNS, failed to have any effect on either the absolute or interpeak latencies or the amplitude of the BAEPs in monkeys. In clinical practice, scopolamine seldom is used alone for premedication. Therefore, we chose to give the monkeys morphine after studying the effect of scopolamine alone to see if a combination of morphine and scopolamine possibly could result in an alteration of the BAEPs. Once again, no change in absolute or interpeak latencies or amplitude of BAEPs was noted. Our findings are in agreement with those of Bhargava *et al.*, who studied the effects of cholinergic drugs on auditory evoked response of rat cerebral cortex. They had shown that late components of evoked

TABLE 4. Amplitude in Microvolts (Mean \pm SD) of Various Waves of BAEPs

| Event | Waves | | | | |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | I | II | III | IV | V |
| Control tracings | 0.42 \pm 0.35 | 0.76 \pm 0.52 | 0.25 \pm 0.15 | 0.45 \pm 0.28 | 0.11 \pm 0.10 |
| 3 Min after 0.1 mg/kg scopolamine | 0.43 \pm 0.32 | 0.68 \pm 0.50 | 0.28 \pm 0.19 | 0.47 \pm 0.19 | 0.08 \pm 0.05 |
| 30 Min after 0.1 mg/kg scopolamine | 0.39 \pm 0.31 | 0.76 \pm 0.39 | 0.32 \pm 0.16 | 0.51 \pm 0.26 | 0.88 \pm 0.05 |
| 3 Min after 0.32 mg/kg scopolamine | 0.38 \pm 0.26 | 0.76 \pm 0.46 | 0.31 \pm 0.17 | 0.54 \pm 0.31 | 0.13 \pm 0.06 |
| 30 Min after 0.32 mg/kg scopolamine | 0.33 \pm 0.22 | 0.72 \pm 0.45 | 0.25 \pm 0.16 | 0.48 \pm 0.21 | 0.14 \pm 0.08 |
| 15 Min after 3.2 mg/kg morphine | 0.38 \pm 0.21 | 0.74 \pm 0.55 | 0.39 \pm 0.23 | 0.62 \pm 0.41 | 0.12 \pm 0.08 |
| P value | 0.6 | 0.9 | 0.7 | 0.8 | * |

* No statistical analysis because this wave could not be defined in 13 out of 60 observations made.

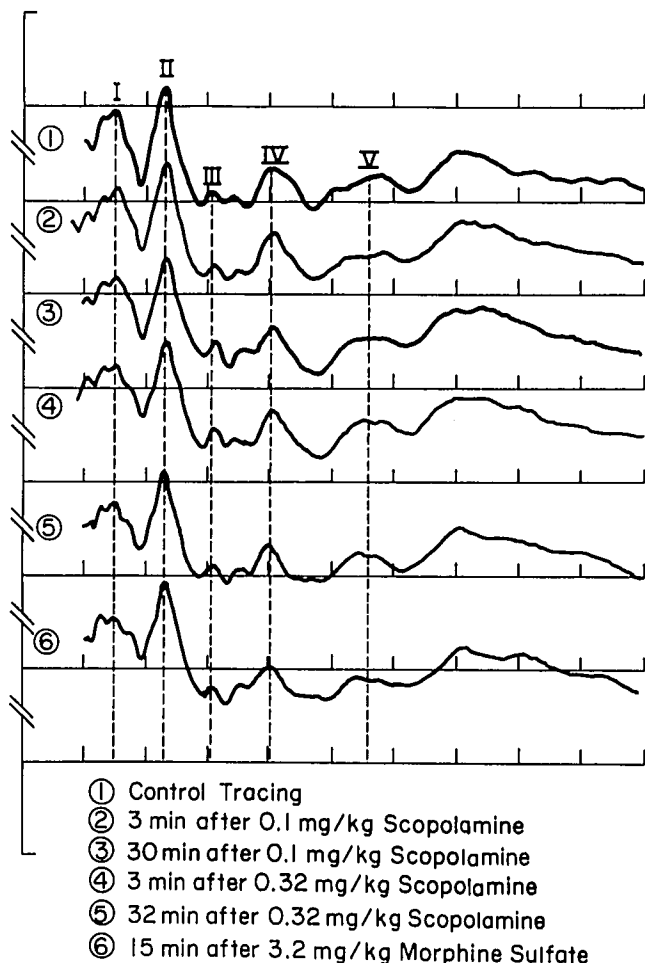


FIG. 3. Effect of scopolamine on morphology and latencies of brain stem auditory evoked potentials. BAEPs tracings from one monkey showing lack of effect of scopolamine and morphine.

response were more responsive to cholinergic drugs than the early components. In their study, the effect of cholinergic agonists were shown to be blocked by prior treatment with scopolamine, while scopolamine alone did not seem to have any significant effect.

Based on the data presented, we conclude that scopolamine, with or without morphine, does not alter the

BAEPs in monkeys. This finding remains to be confirmed in human beings.

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